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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Sheet 2 of the certificate
Page 2 de l'attestation

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Substituted amino isoxazoline derivatives and their use as anti-depressants

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SUBSTITUTED AMINO ISOXAZOLINE DERIVATIVES AND THEIR USE AS
ANTI-DEPRESSANTS

5 The invention concerns substituted amino isoxazoline derivatives, more in particular tricyclic dihydrobenzopyranoisoxazoline, dihydroquinolinoisoxazoline , dihydronaphthalenoisoxazoline and dihydrobenzothiopyranoisoxazoline derivatives substituted on the phenylpart of the tricyclic moiety with primary, secondary and/or tertiary amino groups, processes for their preparation, pharmaceutical compositions
10 comprising them and their use as a medicine, in particular for treating depression, anxiety, movement disorders, psychosis, schizophrenia and body weight disorders including anorexia nervosa and bulimia.

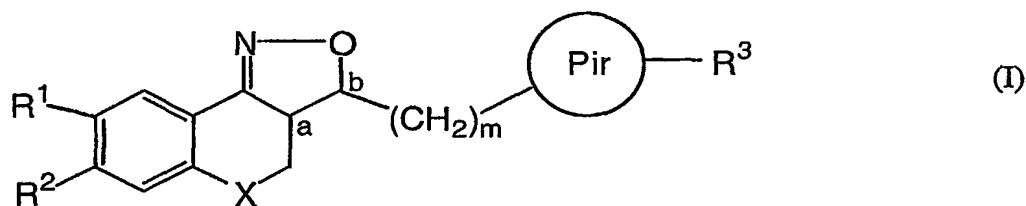
The invention also relates to novel combination of said substituted amino isoxazolines
15 derivatives with antidepressants, anxiolytics, antipsychotics and anti-Parkinson's disease drugs.

Tetrahydronaphthalene and indane derivatives showing anti-depressant activity are known from EP-361 577 B1. These compounds are typical monoamine reuptake
20 blockers with additional α_2 -adrenoceptor antagonist activity and they show anti-depressant activity without being sedative.

The problems associated with the compounds according to the state of the art is that the compounds cause considerable side-effects, such as nausea, excitation, an increased
25 heart rate and a reduced sexual function. Furthermore, it requires a long time, in particular 3-4 weeks, before the response starts.

The purpose of the present invention is to provide novel compounds derivatives for treating depression, anxiety, movement disorders, psychosis, schizophrenia and body
30 weight disorders, in particular compounds that do not exhibit the aforementioned disadvantages.

The present invention relates to novel substituted amino isoxazoline derivatives according to the general Formula (I)



the pharmaceutically acceptable acid or base addition salts thereof, the

5 stereochemically isomeric forms thereof and the *N*-oxide form thereof, wherein :

X is CH₂, N-R⁷, S or O ;

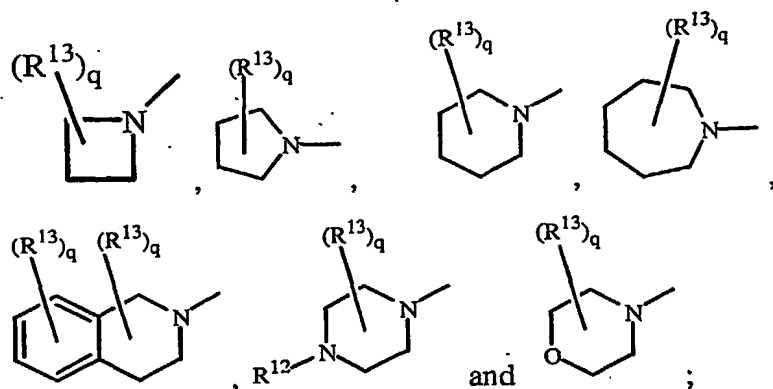
R⁷ is selected from the group of hydrogen, alkyl, Ar¹, Ar¹alkyl, alkylcarbonyl, alkyloxy carbonyl and mono- and di(alkyl)aminocarbonyl ;

10 R¹ and R² are each selected from the group of hydrogen, hydroxy, cyano, halo, OSO₂H, OSO₂CH₃, N-R¹⁰R¹¹, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkylthio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxy carbonyloxy, alkenyloxy, alkenylcarbonyloxy and mono- or di(alkyl)aminoalkyloxy ;

15 with the proviso that at least one of R¹ and R² is N-R¹⁰R¹¹ wherein :

R¹⁰ and R¹¹ are each, independently from each other, selected from the group of hydrogen, alkyl, Ar¹, Ar¹alkyl, pyrrolidinylalkyl, piperidinylalkyl, homopiperidinylalkyl, piperazinylalkyl, morpholinylalkyl, mono- or di(alkyl)aminoalkyl, alkylcarbonyl, alkenylcarbonyl, Ar¹carbonyl, pyridinylcarbonyl, alkyloxy carbonyl, mono- or di(alkyl)aminocarbonyl, mono- or di(Ar¹)aminocarbonyl, mono- or di(alkyloxy carbonylalkyl)aminocarbonyl, pyrrolidinylcarbonyl, aminoiminomethyl, alkylaminoiminomethyl, N-benzylpiperazinylimino-

20 methyl, alkylsulphonyl and Ar¹sulphonyl ; or
25 R¹⁰ and R¹¹ may be taken together and with the N may form a monovalent radical selected from the group of



wherein :

5 R^{12} is selected from the group of hydrogen, alkyl, Ar^1 , Ar^1 alkyl, Ar^1 alkenyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

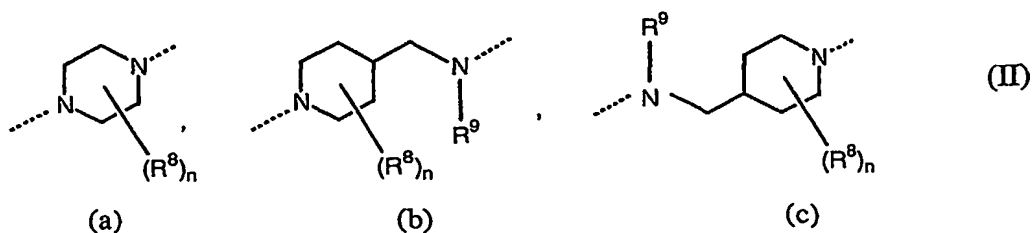
each ring being optionally substituted with q radicals R^{13} , each radical independently from each other selected from the group of alkyl, oxo, Ar^1 , Ar^1 alkyl, Ar^1 alkenyl and alkyloxycarbonyl and q being an integer ranging from 0 to 6 ; or

10 R^1 and R^2 may be taken together to form a bivalent radical $-R^1-R^2-$ selected from the group of $-O-CH_2-NR^{14}-$, $-NR^{14}-CH_2-O-$, $-NR^{15}-CH_2-NR^{14}-$, $-NR^{14}-CH_2-CH_2-O-$, $-O-CH_2-CH_2-NR^{14}-$, $-NR^{15}-CH_2-CH_2-NR^{14}-$, - wherein R^{14} and R^{15} each, independently from each other, are selected from the group of hydrogen, alkyl, Ar^1 , Ar^1 alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

a and b are asymmetric centers ;

15 $(CH_2)_m$ is a straight hydrocarbon chain of m carbon atoms, m being an integer ranging from 1 to 4 ;

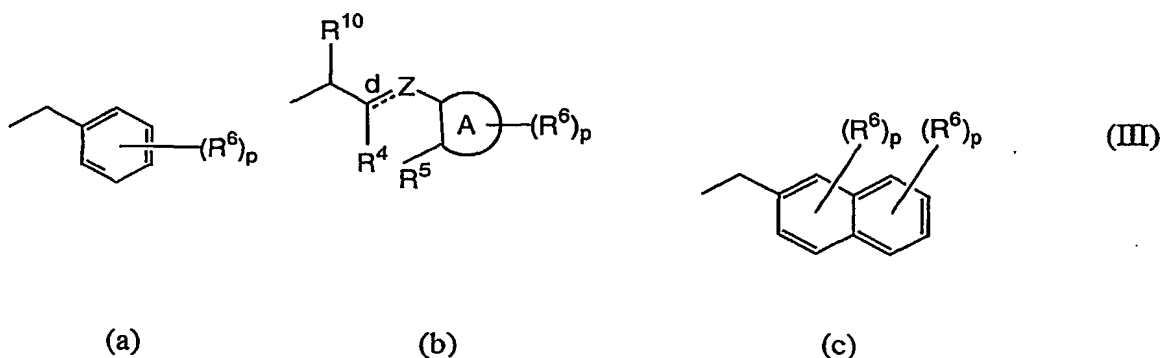
Pir is a radical according to any one of Formula (IIa), (IIb) or (IIc)



- optionally substituted with n radicals R^8 , wherein :
- each R^8 is independently from each other, selected from the group of hydroxy, amino, nitro, cyano, halo and alkyl ;
- 5 n is an integer ranging from 0 to 5 ;
- R^9 is selected from the group of hydrogen, alkyl and formyl ;
- R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system together with an optionally substituted and partially or completely hydrogenated hydrocarbon chain of 1 to 6 atoms long with which said ring system is attached to the Pir radical and of which may contain one or more heteroatoms selected from the group of O, N and S ;
- 10 $alkyl$ represents a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyloxy or amino radicals ;
- 15 $alkenyl$ represents a straight or branched unsaturated hydrocarbon radical having one or more double bonds, optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyloxy or amino radicals ;
- Ar^1 represents phenyl or naphthyl, optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyl, alkyloxy or amino radicals.
- 20

More in particular, the invention relates to compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, wherein R^3 is a radical according to any one of Formula (IIIa), (IIIb) or (IIIc)

25



wherein :

- d is a single bond while Z is a bivalent radical selected from the group of
 5 -CH₂-, -C(=O)-, -CH(OH)-, -C(=N-OH)-, -CH(alkyl)-, -O-, -S-, -S(=O)-, -NH- and -SH-; or d is a double bond while Z is a trivalent radical of formula =CH- or =C(alkyl)- ;
- A is a 5- or 6-membered aromatic homocyclic or heterocyclic ring, selected from the group of phenyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl,
 10 pyridazinyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, oxadiazolyl and isoxazolyl ;
- p is an integer ranging from 0 to 6 ;
- R⁴ and R⁵ are each, independently from each other, selected from the group of hydrogen, alkyl, Ar¹, biphenyl, halo and cyano ; or
- 15 R⁴ and R⁵ may be taken together to form a bivalent radical -R⁴-R⁵- selected from the group of -CH₂-, =CH-, -CH₂-CH₂-, -CH=CH-, -O-, -NH-, =N-, -S-, -CH₂N(-alkyl)-, -N(-alkyl)CH₂-, -CH₂NH-, -NHCH₂-, -CH=N-, -N=CH-, -CH₂O- and -OCH₂- ;
- each R⁶ is independently from each other, selected from the group of hydroxy, amino, nitro, cyano, halo, carboxyl, alkyl, Ar¹, alkyloxy, Ar¹oxy, alkyl-carbonyloxy, alkyloxycarbonyl, alkylthio, mono- and di(alkyl)amino, alkylcarbonylamino, mono- and di(alkyl)aminocarbonyl, mono- and di(alkyl)aminocarbonyloxy, mono- and di(alkyl)aminoalkyloxy ; or
- 20 two vicinal radicals R⁶ may be taken together to form a bivalent radical -R⁶-R⁶- selected from the group of -CH₂-CH₂-O-, -O-CH₂-CH₂-, -O-CH₂-C(=O)-, -C(=O)-CH₂-O-, -O-CH₂-O-, -CH₂-O-CH₂-, -O-CH₂-CH₂-O-, -CH=CH-CH=CH-, -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-C(=O)-, -C(=O)-CH₂-CH₂-, -CH₂-C(=O)-CH₂- and -CH₂-CH₂-CH₂-CH₂- ; and
- 30 R¹⁰ is selected from the group of hydrogen, alkyl, Ar¹ and Ar¹alkyl.

Preferably, the invention relates to those compounds according to Formula (I), the

pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, wherein $X=O$ or NH ; $m = 1$; Pir is a radical according to Formula (IIa) wherein $n = 0$; R^3 is a radical according to Formula (IIIb) wherein Z is $=CH-$, d is a double bond, A is a phenyl ring, R^4 is hydrogen or alkyl and R^5 and R^{10} are each hydrogen.

More preferably, the invention relates to compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, where $X=O$, one of R^1 and R^2 is hydrogen, methoxy or ethoxy; $m = 1$; Pir is a radical according to Formula (IIa) wherein $n = 0$; R^3 is a radical according to Formula (IIIb) wherein Z is $=CH-$, d is a double bond, A is a phenyl ring, R^4 is methyl and R^5 and R^{10} are each hydrogen.

Particularly interesting are compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof where R^1 is hydrogen or methoxy and R^2 is an amine radical $NR^{10}R^{11}$, $X=O$, $m = 1$; Pir is a radical according to Formula (IIa) wherein $n = 0$; R^3 is a radical according to Formula (IIIb) wherein Z is $=CH-$, d is a double bond, A is a phenyl ring, R^4 is methyl and R^5 and R^{10} are each hydrogen.

Particularly interesting compounds are those compounds in which A is an unsubstituted phenyl ring or a phenyl ring substituted with a halo atom, in particular with F , Cl or Br .

Particularly interesting compounds are those compounds in which $NR^{10}R^{11}$ is

In the framework of this application, alkyl defines straight or branched saturated hydrocarbon radicals having from 1 to 6 carbon atoms, for example methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl; or alkyl defines cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms, for example cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Alkyl radicals may be optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyloxy or amino radicals, for example polyhaloalkyl, in particular difluoromethyl and

trifluoromethyl.

In the framework of this application, halo is generic to fluoro, chloro, bromo and iodo.

5 In the framework of this application, alkenyl represents a straight or branched unsaturated hydrocarbon radical having one or more double bonds, for example ethenyl, 1-propenyl, 2-propenyl and 1,3-butanedieryl. Alkenyl radicals may be optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyloxy or amino radicals, for example hydroxyethenyl.

10

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for
15 example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic
20 acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms by treatment with appropriate organic and inorganic bases. Appropriate base salts
25 forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

30 Conversely, said salts forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

5 The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more nitrogens of the piperazinyl radical are *N*-oxidized.

10 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular,
15 stereogenic centers may have the *R*- or *S*-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Compounds encompassing double bonds can have an *E* or *Z*-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of Formula (I) are obviously intended to be embraced within the scope of this invention.

20 Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using
25 relative descriptors [*R**,*R**] or [*R**,*S**], where *R** is always specified as the reference center and [*R**,*R**] indicates centers with the same chirality and [*R**,*S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R**,*S**]. If "α" and "β" are used : the position of the highest priority
30 substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric

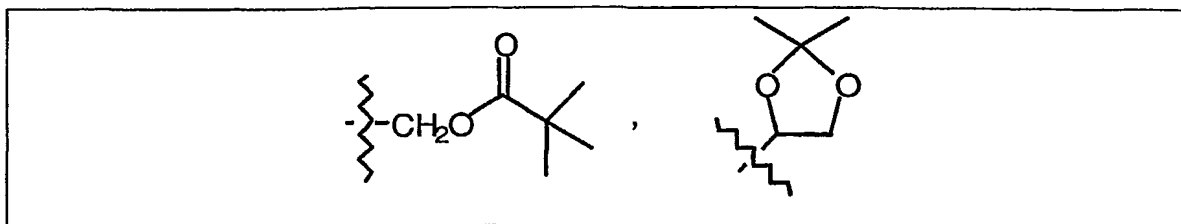
carbon atom in the ring system (hydrogen atom in compounds of Formula(I)) relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

5

Compounds of Formula (I) and some of the intermediates have at least two stereogenic centers in their structure, respectively denoted a and b in Formula (I). Due to the synthetic pathway followed for the synthesis of the tricyclic system, the configuration of those two asymmetric centers a and b is predetermined, so that the relative
10 configuration of center a is S* and of center b is R*.

The invention also comprises derivative compounds (usually called "prodrugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Prodrugs are usually (but not
15 always) of lower potency at the target receptor than the compounds to which they are degraded. Prodrugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further
20 discussion on prodrugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, 29, pp. 455-473.

Prodrugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable
25 acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula -COOR^x, where R^x is a C₁₋₆alkyl, phenyl, benzyl or one of the following groups :



Amidated groups include groups of the formula $\text{-CONR}^y\text{R}^z$, wherein R^y is H, C_{1-6} alkyl, phenyl or benzyl and R^z is -OH , H, C_{1-6} alkyl, phenyl or benzyl. .

- 5 Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

10 The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are
15 liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific
20 stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

25 The compounds according to the invention, in particular compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, have surprisingly been shown to have selective serotonin (5-HT) reuptake inhibitor activity in combination with additional α_2 -adrenoceptor antagonist activity and show a strong

anti-depressant and/or anxiolytic activity and/or antipsychotic and/or a body weight control activity without being sedative. Also, in view of their selective serotonin (5-HT) reuptake inhibitor as well as α_2 -adrenoceptor antagonist activity, compounds according to the invention are also suitable for treatment and/or prophylaxis in diseases where either one of the activities alone or the combination of said activities may be of therapeutic use. In particular, the compounds according to the invention may be suitable for treatment and/or prophylaxis in the following diseases :

- Central nervous system disorders, including :
 - Mood disorders, including particularly major depressive disorder, depression with or without psychotic features, catatonic features, melancholic features, atypical features of postpartum onset and, in the case of recurrent episodes, with or without seasonal pattern, dysthymic disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, recurrent brief depressive disorder, mixed affective disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, substance-induced mood disorder, mood disorder not otherwise specified, seasonal affective disorder and premenstrual dysphoric disorders.
 - Anxiety disorders, including panic attack, agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified.
 - Stress-related disorders associated with depression and/or anxiety, including acute stress reaction, adjustment disorders (brief depressive reaction, prolonged depressive reaction, mixed anxiety and depressive reaction, adjustment disorder with predominant disturbance of other emotions, adjustment disorder with predominant disturbance of conduct, adjustment disorder with mixed disturbance of emotions and conduct, adjustment disorders with other specified predominant symptoms) and other reactions to severe stress.
 - Dementia, amnesic disorders and cognitive disorders not otherwise specified, especially dementia caused by degenerative disorders, lesions, trauma,

- infections, vascular disorders, toxins, anoxia, vitamin deficiency or endocrinic disorders, or amnesic disorders caused by alcohol or other causes of thiamin deficiency, bilateral temporal lobe damage due to Herpes simplex encephalitis and other limbic encephalitis, neuronal loss secondary to anoxia / hypoglycemia
- 5 / severe convulsions and surgery, degenerative disorders, vascular disorders or pathology around ventricle III.
- Cognitive disorders due to cognitive impairment resulting from other medical conditions.
 - Personality disorders, including paranoid personality disorder, schizoid
 - 10 personality disorder, schizotypal personality disorder, antisocial personality disorder, borderline personality disorder, histrionic personality disorder, narcissistic personality disorder, avoidant personality disorder, dependent personality disorder, obsessive-compulsive personality disorder and personality disorder not otherwise specified.
 - Schizoaffective disorders resulting from various causes, including
 - 15 schizoaffective disorders of the manic type, of the depressive type, of mixed type, paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, substance-induced
 - 20 psychotic disorder and psychotic disorder not otherwise specified.
 - Akinesia, akinetic-rigid syndromes, dyskinesia and medication-induced parkinsonism, Gilles de la Tourette syndrome and its symptoms, tremor, chorea, myoclonus, tics and dystonia.
 - Attention-deficit / hyperactivity disorder (ADHD).
 - Parkinson's disease, drug-induced Parkinsonism, post-encephalitic
 - 25 Parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification.
 - Dementia of the Alzheimer's type, with early or late onset, with depressed
 - 30 mood.
 - Behavioral disturbances and conduct disorders in dementia and the mentally retarded, including restlessness and agitation.

- Extra-pyramidal movement disorders.
- Down's syndrome.
- Akathisia.
- Eating Disorders, including anorexia nervosa, atypical anorexia nervosa,
5 bulimia nervosa, atypical bulimia nervosa, overeating associated with other
psychological disturbances, vomiting associated with other psychological
disturbances and non-specified eating disorders.
- AIDS-associated dementia.
- Chronic pain conditions, including neuropathic pain, inflammatory pain, cancer
10 pain and post-operative pain following surgery, including dental surgery. These
indications might also include acute pain, skeletal muscle pain, low back pain,
upper extremity pain, fibromyalgia and myofascial pain syndromes, orofascial pain,
abdominal pain, phantom pain, tic douloureux and atypical face pain, nerve root
damage and arachnoiditis, geriatric pain, central pain and inflammatory pain.
- 15 • Neurodegenerative diseases, including Alzheimer's disease, Huntington's chorea,
Creutzfeld-Jacob disease, Pick's disease, demyelinating disorders, such as multiple
sclerosis and ALS, other neuropathies and neuralgia, multiple sclerosis,
amyotropical lateral sclerosis, stroke and head trauma.
- Addiction disorders, including :
20 • Substance dependence or abuse with or without physiological dependence,
particularly where the substance is alcohol, amphetamines, amphetamine-like
substances, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine,
opioids, phencyclidine, phencyclidine-like compounds, sedative-hypnotics,
benzodiazepines and/or other substances, particularly useful for treating
25 withdrawal from the above substances and alcohol withdrawal delirium.
- Mood disorders induced particularly by alcohol, amphetamines, caffeine,
cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine,
sedatives, hypnotics, anxiolitics and other substances.
- Anxiety disorders induced particularly by alcohol, amphetamines, caffeine,
30 cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine,
sedatives, hypnotics, anxiolitics and other substances and adjustment disorders
with anxiety.

- Smoking cessation.
- Body weight control, including obesity.
- Sleep disorders and disturbances, including :
 - Dyssomnias and/or parasomnias as primary sleep disorders, sleep disorders
5 related to another mental disorder, sleep disorder due to a general medical
condition and substance-induced sleep disorder.
 - Circadian rhythms disorders.
 - Improving the quality of sleep.
- Sexual dysfunction, including sexual desire disorders, sexual arousal disorders,
10 orgasmic disorders, sexual pain disorders, sexual dysfunction due to a general
medical condition, substance-induced sexual dysfunction and sexual dysfunction
not otherwise specified.

The present invention thus also relates to compounds of Formula (I), the
15 pharmaceutically acceptable acid or base addition salts thereof, the stereochemically
isomeric forms thereof, the *N*-oxide form thereof, as well as the pro-drugs thereof for
use as a medicine, in particular for treating depression, anxiety, movement disorders,
psychosis, Parkinson's disease and body weight disorders.

20 The invention also relates to a pharmaceutical composition comprising a
pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective
amount of a compound according to the invention, in particular a compound according
to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the
stereochemically isomeric forms thereof and the *N*-oxide form thereof or a prodrug as
25 defined above.

The compounds of the invention, in particular the compounds according to Formula (I),
the pharmaceutically acceptable acid or base addition salts thereof, the
stereochemically isomeric forms thereof and the *N*-oxide form thereof and the
30 prodrugs, or any subgroup thereof may be formulated into various pharmaceutical
forms for administration purposes. As appropriate compositions there may be cited all
compositions usually employed for systemically administering drugs. To prepare the

pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration.

5 These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, 10 syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the 15 carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like 20 may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a 25 significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

30 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary

dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, 5 injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds according to the invention may also be suitable as add-on treatment and/or prophylaxis in the above listed diseases in combination with any combination of compounds selected from the group of antidepressants, anxiolytics, antipsychotics 10 and/or anti-Parkinson's disease drugs which are currently available or in development or which will become available in the future, to improve efficacy and/or onset of action. This is evaluated in rodent models in which antidepressants, anxiolytics, antipsychotics and/or anti-Parkinson's disease drugs are shown to be active. For example, compounds are evaluated in combination with antidepressants, anxiolytics, 15 antipsychotics and/or anti-Parkinson's disease drugs for attenuation of stress-induced hyperthermia.

The invention therefore also relates to a pharmaceutical composition comprising the compounds according to the invention, in particular the compounds according to 20 Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, and the prodrugs and one or more other compounds selected from the group of antidepressants, anxiolytics, antipsychotics and/or anti-Parkinson's disease drugs.

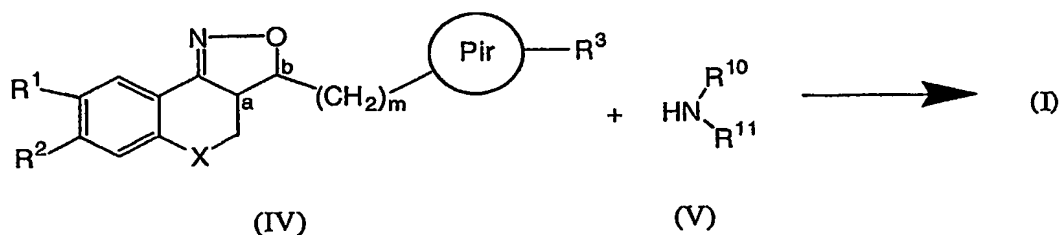
25 The invention further relates to a process for making a pharmaceutical composition comprising mixing a compound according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, and the prodrugs, or any subgroup thereof and a compound selected from the group of 30 antidepressants, anxiolytics, antipsychotics and anti-Parkinson's disease drugs and a pharmaceutically acceptable carrier.

The invention also relates to the use of a compound according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, and the prodrugs, for the manufacture of a medicament for
 5 treating depression, anxiety, movement disorders, psychosis, schizophrenia and body weight disorders.

In vitro receptor and neurotransmitter transporter binding and signal-transduction studies can be used to evaluate the α_2 -adrenoceptor antagonism activity and serotonin
 10 (5-HT) reuptake inhibitor activity of the present compounds. As indices for central penetration and potency to block the α_2 -adrenoceptors and serotonin transporters, respectively, *ex vivo* α_2 -adrenoceptor and serotonin transporter occupancy can be used. As indices of α_2 -adrenoceptor antagonism *in vivo*, the reversal of the loss of righting reflex, observed in rats after subcutaneous injection or oral dosage of the compound
 15 before intravenous medetomidine administration in rats can be used (medetomidine-test). As indices of serotonin (5-HT) reuptake inhibition activity, the inhibition of head-twitches and excitation in rats, observed after subcutaneous injection or oral dosage of the compound before subcutaneous p-chloroamphetamine administration in rats can be used (pCA-test).

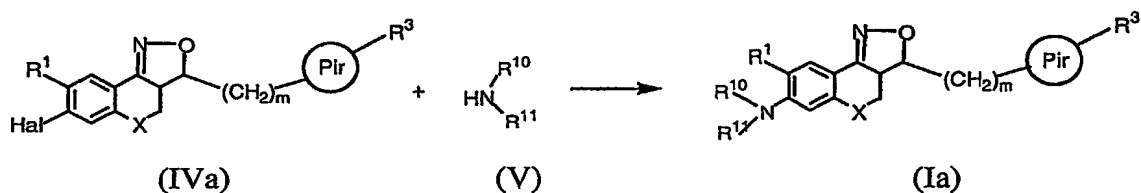
20 The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

In particular, the compounds according to Formula (I) can be prepared by a reaction
 25 (generally called a nucleophilic aromatic substitution reaction) with an amine of Formula (V) on an intermediate according to Formula (IV),

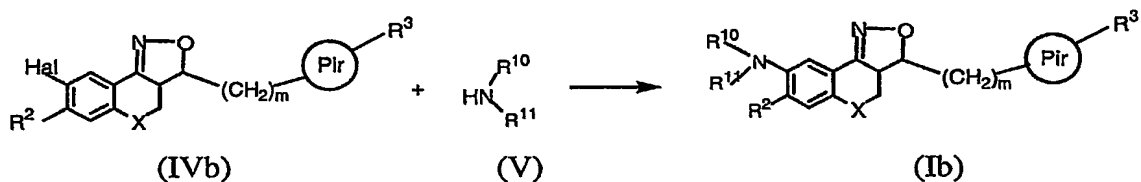


wherein all variables, except for R^1 and R^2 , have the same meaning as in Formula (I), at least one of R^1 and R^2 is an halogen and at most one of R^1 and R^2 is selected from the group of hydrogen, hydroxy, cyano, halo, OSO_2H , OSO_2CH_3 , $N-R^{10}R^{11}$, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkythio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenylcarbonyloxy and mono- or di(alkyl)amino-alkyloxy.

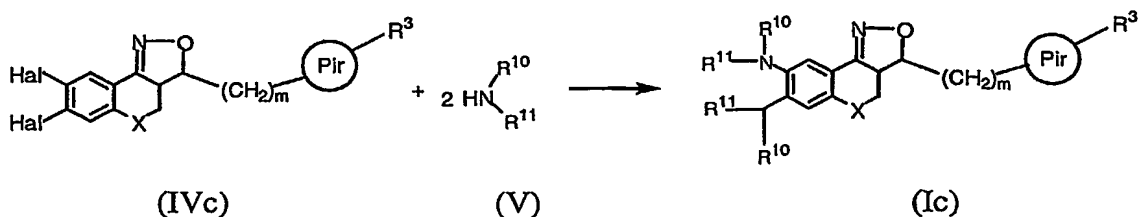
10 Such a reaction can also be formulated either as



or as



15 or as



Said reaction may be carried out in a reaction inert solvent such as pyridine, in the

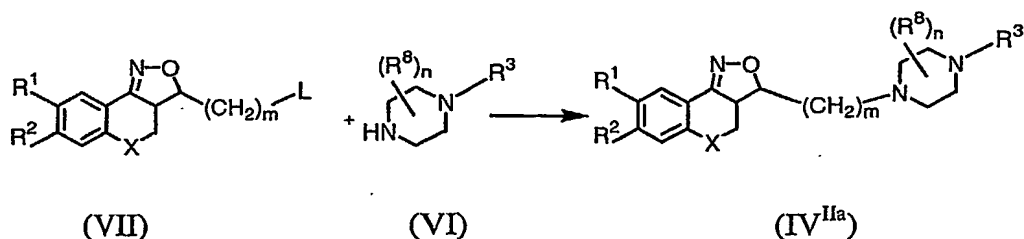
presence of a suitable base such as KF and at a temperature between room and reflux temperature.

5 The substituents R^1 and R^2 may be changed or interconverted into each other by methods well known in the art, such as demethylation, acylation, esterification, amination and amidation. In particular, some of the reactions known to apply for the reduction of secondary amines can be applied, for instance the reduction of a benzylamine radical to the corresponding amine-radical using for instance HBr and acetic acid or the synthesis of a secondary amine radical from a primary amine radical
10 by the reaction with an isocyanate or an acylhalide in an appropriate reaction-inert solvent, such as trichloromethane in the presence of a suitable base, such as triethylamine.

The starting materials and some of the intermediates are compounds that are either
15 commercially available or may be prepared according to conventional reaction procedures generally known in the art.

The intermediate compounds, in particular the intermediate compounds according to Formula (IV), more in particular according to Formula (IVa), (IVb) and (IVc) can be
20 prepared according to various ways.

In particular, the intermediate compounds according to Formula (IV^{IIa}), i.e. intermediate compounds according to Formula (IV) with a Pir-radical according to Formula (IIa) can be prepared by a nucleophilic substitution reaction with a substituted
25 piperazine according to Formula (VI) on an intermediate compound of Formula (VII). These reactions may be carried out in a reaction inert solvent such as dioxane, methylisobutylketone or *N,N'*-dimethylformamide, in the presence of a suitable base such as potassium carbonate, sodium carbonate or triethylamine, or even without a base, using in this latter case excess of reagent of Formula (VI). Convenient reaction
30 temperatures range between 100°C and 150°C.

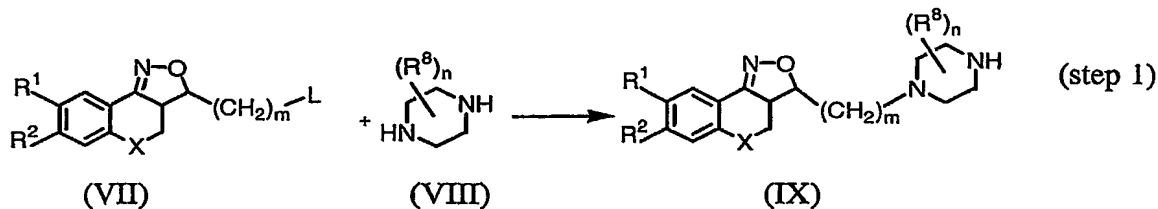


In the intermediate compound of Formula (VII), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy.

5

The compounds according to Formula (IV^{IIa}) can also be prepared by a 2-step reaction scheme in which an intermediate compound of Formula (VII) is first reacted (step 1) with a substituted piperazine according to Formula (VIII) after which the R³-radical is introduced into the resulting intermediate compound of Formula (IX) (step 2). Reaction conditions are similar to those described above for intermediate compounds of Formula (IV^{IIa}).

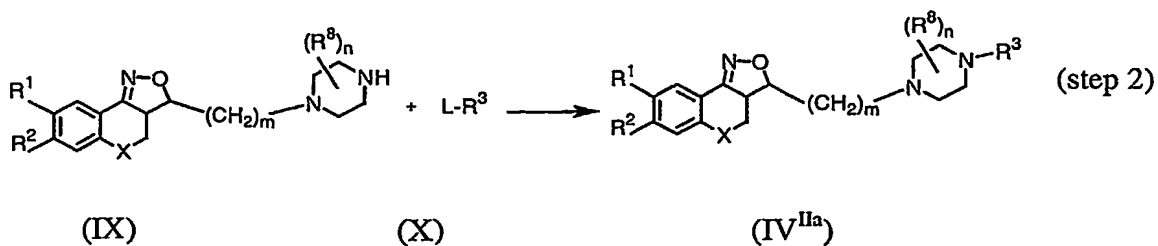
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In intermediate compound of Formula (VII), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy.

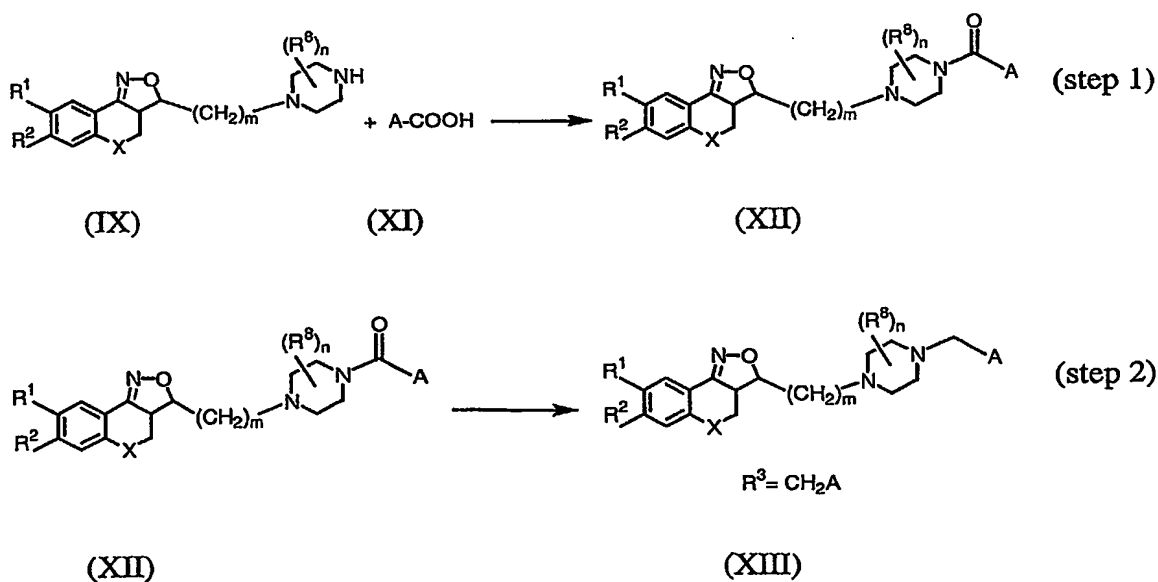
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One of the nitrogen functions of the substituted piperazine of Formula (VIII) may also be protected, e.g. by a tert-butyloxycarbonyl-group.



In the compound of Formula (X), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy. Also, $R^3\text{-CHO}$ may be used instead of a compound of Formula (X) wherein R^3 has the same meaning as in Formula (I).

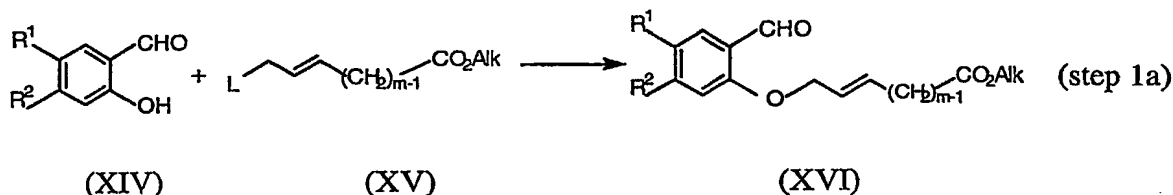
The compounds according to Formula (IV^{IIa}) can also be prepared by a 2-step reaction scheme in which an intermediate of Formula (IX) is reacted with an acid according to Formula (XI) (step 1), followed by a subsequent reduction of the carbonyl-function of the intermediate compound of Formula (XII) (step 2). Reactions of step 1 may be carried out in a reaction inert solvent, such as chloroform, dichloromethane, tetrahydrofuran, dimethylformamide or a mixture thereof, using any of methods known to a person skilled in the art using condensation reagents such as 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide or by previous transformation of carboxylic acid of Formula (XI) into its corresponding acid chloride. Reactions shown in step 2 can be performed using a suitable reducing agent, such as lithium-aluminum hydride or aluminum hydride, in a suitable solvent, for example tetrahydrofuran. Generally, these reactions are run at a temperature ranging between -20°C and room temperature.



In the intermediate compounds of Formula (XI), (XII) and (XIII), the A-group represents an optionally substituted aromatic homocyclic or heterocyclic ring system including a partially or completely hydrogenated hydrocarbon chain of maximum 5 atoms long of which one or more carbon atoms may be replaced by one or more atoms selected from the group of oxygen, nitrogen and sulphur, with which the ring system is attached to the Pir radical that has been defined above.

Intermediate compounds of Formula (VII) in which X=O may be prepared according to the following reaction scheme :

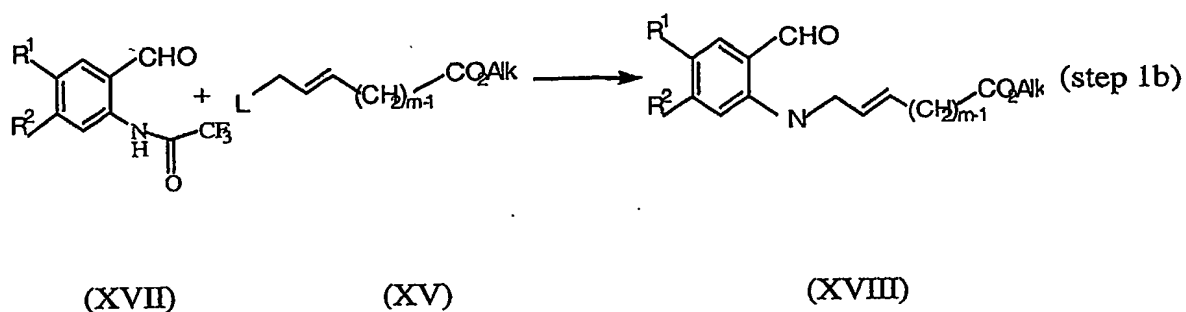
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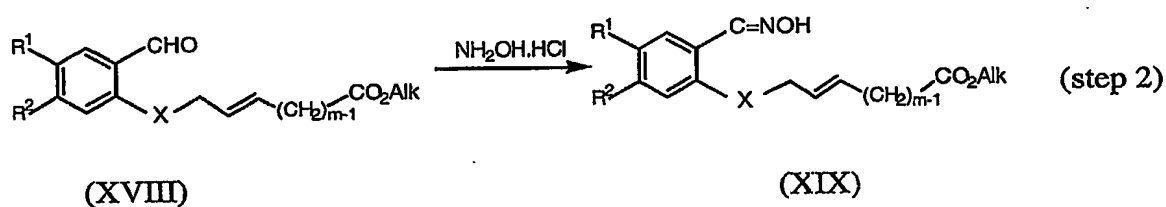
In intermediate compound of Formula (XV), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulfonyloxy or 4-methylbenzenesulfonyloxy. Furthermore, Alk in intermediate compound of Formula (XV) represents any C₁₋₆ alkyl-group, in particular an ethyl-group and m is defined as in Formula (I).

Intermediates according to Formula (VII) in which X=NH may also be prepared in an equivalent manner according to above step 1a, provided that the intermediate compound of Formula (XIV) is replaced by its amine-analog of Formula (XVII), preferably with the amine group protected with e.g. a COCF₃- group. The alkylation step may be carried out in a reaction inert solvent, for example, tetrahydrofuran or dimethylformamide, in the presence of a strong base, such as sodium or potassium hydride, and the addition of a crown-ether, such as 18-crown-6 or 15-crown-5.

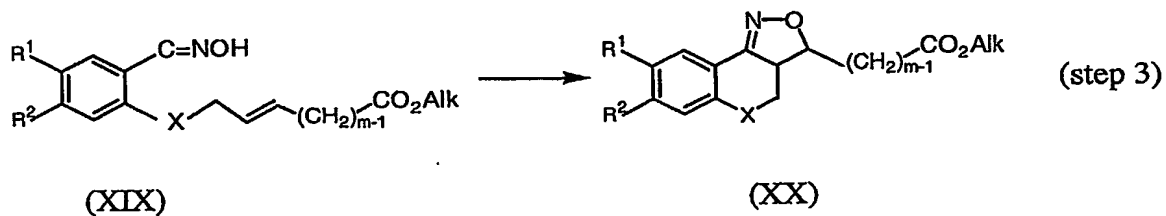
Convenient reaction temperatures range between room temperature and 60°C.



Intermediates of Formula (XVIII) are converted to oximes of Formula (XIX) using art-known techniques, such as using hydroxylamine hydrochloride in the presence of
 5 NaHCO_3 or pyridine in a reaction inert solvent, for example ethanol (step 2).



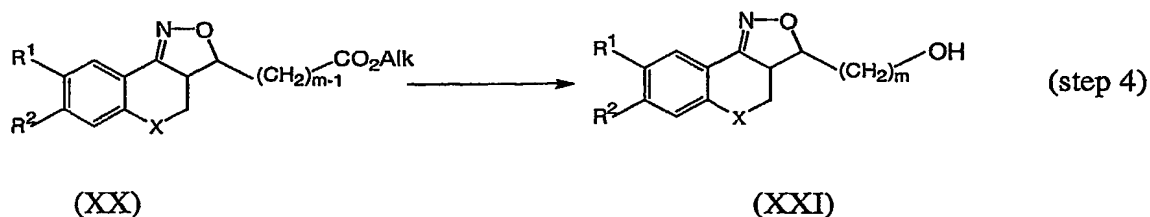
Intermediate compounds of Formula (XIX) are oxidized to their nitril oxides and undergoes *in situ* an intramolecular cycloaddition, yielding intermediate compounds of
 10 Formula (XX). This oxidation can be carried out using a sodium hypochlorite solution in the presence of triethylamine in an inert solvent such as dichloromethane at room temperature. Oxidation can also be performed using Chloramine-T (*N*-chloro-4-methyl-benzenesulfonamide, sodium salt), stirring and heating in a solvent such as refluxing ethanol. At this stage the two stereocenters a and b of Formula (IV) are
 15 formed.



Preparation of an intermediate compound of Formula (XXI) can be achieved using

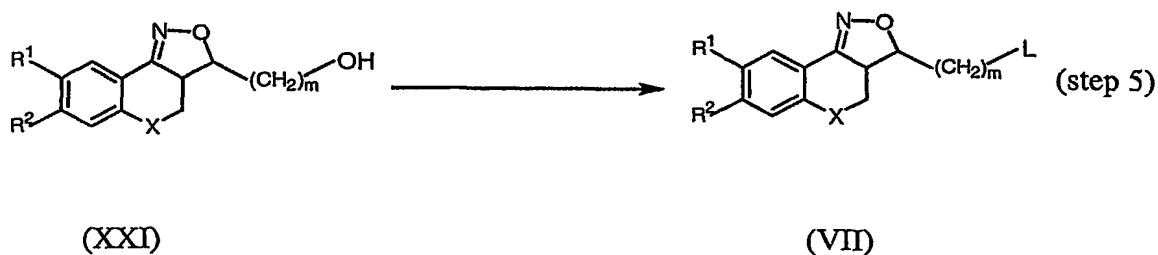
procedures known in the art, for instance by reduction of the carbonyl compound of Formula (XX) in the presence of a suitable reducing agent, for example, sodiumborohydride in a suitable solvent, such as water, an alcohol, tetrahydrofuran or a mixture thereof, generally at room temperature.

5



The intermediate compound of Formula (VII) can be prepared from intermediate compound of Formula (XXI) using standard techniques. Thus, reaction with methanesulfonyl chloride or 4-methylbenzenesulfonyl chloride in the presence of a base, such as triethylamine, in a reaction inert solvent, for example dichloromethane, at reaction temperatures ranging between 0°C and room temperature, yields the corresponding sulfonyloxy derivative intermediate compound of Formula (VII). The corresponding halo-derivative can also be prepared, e.g. treating intermediate compound of Formula (XXI) with triphenylphosphine, in the presence of tetrachloromethane, in a reaction inert solvent, such as tetrahydrofuran, stirring and refluxing the mixture.

15



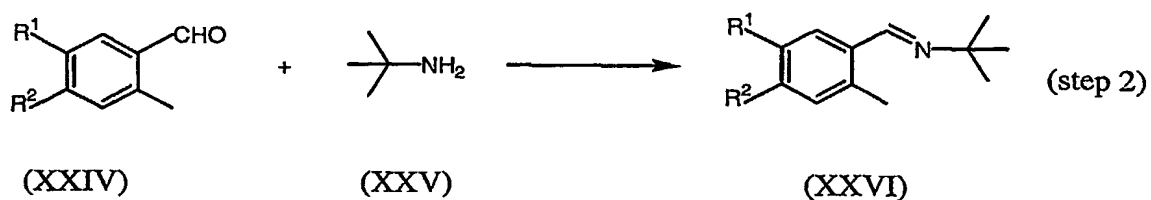
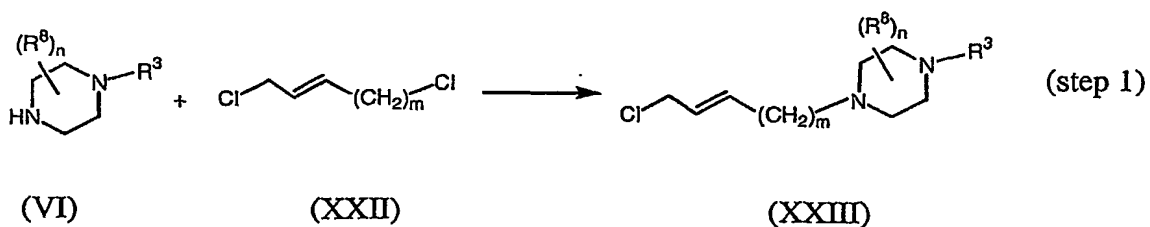
20 It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one

enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC. Typically, intermediate compounds (VII) and (IV) and final compounds according to Formula (I) may be separated into their enantiomeric forms.

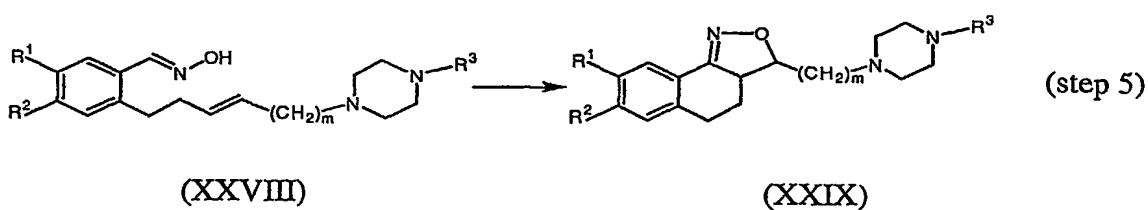
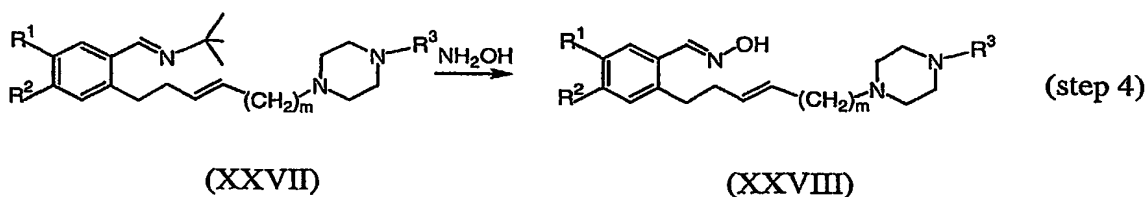
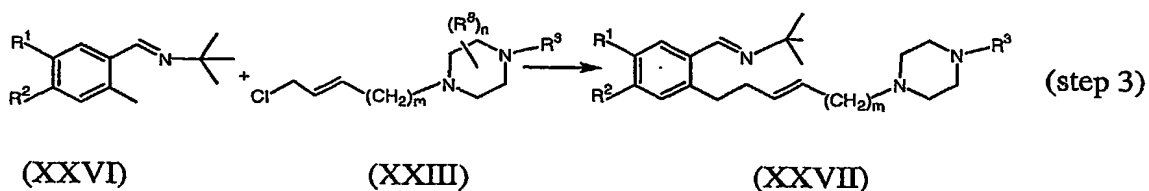
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Compounds according to the invention in which $X=CH_2$ may be prepared according to the following reaction scheme (Scheme 1) in which an intermediate compound according to Formula (VI) is first *N*-alkylated with a dihaloderivative of Formula (XXII) using standard techniques, in the presence or absence of a base and in an inert
10 reaction solvent, such as chloroform, dichloromethane or 1,2-dichloroethane, and at reaction temperatures ranging between room temperature and 80°C, yielding an intermediate compound of Formula (XXIII). An aldehyde of Formula (XXIV) is reacted with *tert*-butylamine (XXV) in an aprotic solvent such as toluene, stirring and heating at reflux temperature with removal of water using a standard device, such as a
15 Dean-Stark water separator, yielding an imine of Formula (XXVI). C-alkylation of intermediate compound of Formula (XXVI) with intermediate compound of Formula (XXIII) can be achieved in the presence of an alkyl-lithium derivative, such as *n*-butyllithium, under an inert atmosphere and in a dry inert solvent, such as tetrahydrofuran, at low temperatures ranging between -78°C and 0°C, yielding an
20 intermediate compound of Formula (XXVII). The intermediate compound of Formula (XXVIII) may be prepared by reaction of intermediate compound of Formula (XXVII) with hydroxylamine, in the presence of a base such as sodium bicarbonate, in a solvent such as a lower alkyl-alcohol like ethanol, generally at room temperature. Finally, the oxidation of the oxime derivative of Formula (XXVIII) to its nitril oxide and
25 subsequent *in situ* cycloaddition to give an intermediate compound of Formula (XXIX), may be achieved by similar standard techniques such as those described above for intermediate compound of Formula (XIX) to give intermediate compounds of Formula (XX).

Schema 1



5



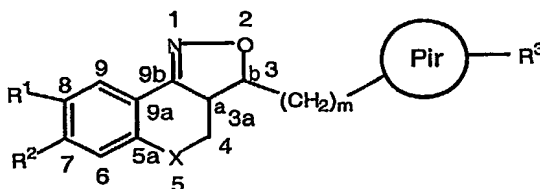
- 10 It is evident that the reaction steps disclosed above may be adapted to the specific reaction products. The reaction steps disclosed may be performed in any way known to the skilled person, including in solution or as solid phase reactions, the latter during

which the reaction products are bound to a resin material and are - in a final cleavage step - released from the resin material. Examples of such embodiments and adaptations have been disclosed by way of the Examples further in this application.

- 5 The following examples illustrate the present invention without being limited thereto.

Experimental part

- 10 The carbon ring numbering system for the compounds according to Formula (I) used in this application is as follows :



- 15 Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray
20 diffraction. The stereogenic centers a and b in compounds of Formula (I) have respectively the ring numbers 3a and 3.

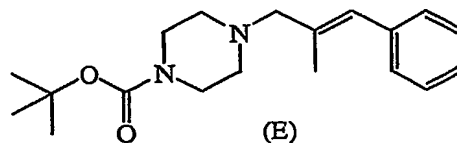
Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropyl ether, and "THF" is defined as tetrahydrofuran.

25

A. Preparation of the intermediates

Example A.1

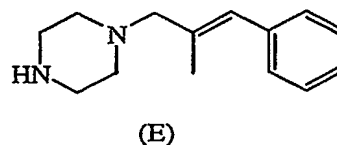
a. Preparation of intermediate 1



- 30 A mixture of (3-chloro-2-methyl-1-propenyl)benzene (0.0506 mol), 1,1-dimethylethyl 1-piperazinecarboxylate (0.076 mol) and NaHCO₃ (0.0506 mol) in CHCl₃ (150 ml) was stirred and refluxed for 9 hours. The reaction mixture was treated with water and this

mixture was extracted with CH_2Cl_2 . The residue was purified by short open column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1). The pure fractions were collected and the solvent was evaporated. Yield: 16.7 g of intermediate 1 (98%).

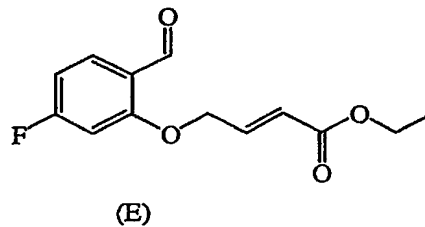
b. Preparation of intermediate 2



- 5 Trifluoroacetic acid (81 ml) was added dropwise to a solution of intermediate 1 (0.0496 mol) in CH_2Cl_2 (350 ml) and the resulting reaction mixture was stirred for 4 hours at room temperature. The reaction mixture was cooled and alkalized with 50% NaOH. This mixture was extracted and the organic solvent was vaporated. Yield: 9.6 g of intermediate 2.

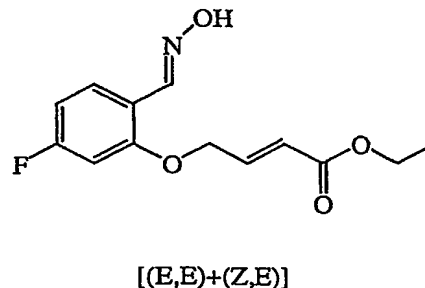
10 Example A.2

a. Preparation of intermediate 3



- K_2CO_3 (0.0265 mol) and ethyl (E)-4-bromo-2-butenolate (0.02145 mol) were added to a solution of 4-fluoro-2-hydroxybenzaldehyde (0.0143 mol) in DMF (16 ml), stirred at 0°C . The reaction mixture was stirred for 5 hours at room temperature. Water was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2 /hexane 1/1 and 2/1). The desired fractions were collected and the solvent was evaporated. Yield: 3.47 g of intermediate 3.

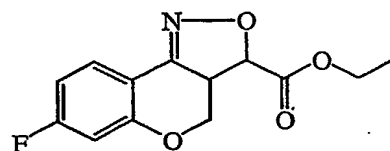
b. Preparation of intermediate 4



- 20 NaOAc (0.0207 mol) and hydroxylamine (0.0165 mol) were added to a solution of intermediate 3 (0.0138 mol) in ethanol (35 ml), stirred at 0°C . The reaction mixture was stirred for 2 hours at 0°C . Then, CH_2Cl_2 and water were added. The mixture was neutralized with a saturated aqueous NaHCO_3 solution. The organic layer was

separated, dried (Na_2SO_4), filtered and the solvent was evaporated. Yield: 4.65 g intermediate 4.

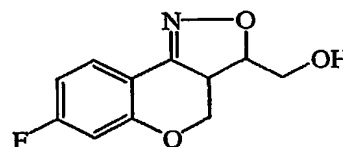
c. Preparation of intermediate 5



(CIS)

NaClO, 4% (0.0348 mol) was added dropwise to a solution of intermediate 4 (0.0174 mol) in CH_2Cl_2 (70 ml), at 0 °C. The reaction mixture was stirred for 2 hours at room temperature. Et_3N (0.0261 mol) was added dropwise at 0 °C and the resulting reaction mixture was stirred for 24 hours at room temperature. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 100/0, then 90/10). The product fractions were collected and the solvent was evaporated. Yield: 1.2 g of intermediate 5 (26%).

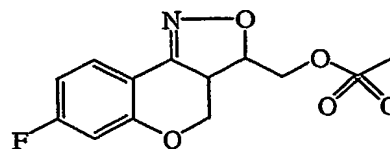
d. Preparation of intermediate 6



(CIS)

NaBH_4 (0.0105 mol) was added portionwise to a solution of intermediate 5 (0.0042 mol) in THF (32 ml) and H_2O (3 ml), at 0 °C. The reaction mixture was stirred for 24 hours at room temperature. A saturated aqueous NH_4Cl solution was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 9/1 and $\text{CH}_2\text{Cl}_2/2$ -propanone 4/1). The desired fractions were collected and the solvent was evaporated. Yield: 0.76 g of intermediate 6 (81%).

e. Preparation of intermediate 7



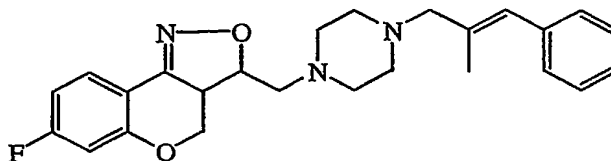
(CIS)

At 0 °C, methanesulfonyl chloride (0.003696 mol) was added to a solution of intermediate 6 (0.00336 mol) and Et_3N (0.00504 mol) in CH_2Cl_2 (15 ml). The reaction

mixture was stirred for 60 minutes at 0°C. CH₂Cl₂ was added. A saturated aqueous NaHCO₃ solution was added. The organic layer was separated, dried (Na₂SO₄), filtered and the solvent was evaporated. Yield: 0.890 g of intermediate 7 (88%).

5 Example A.3

Preparation of intermediate 8

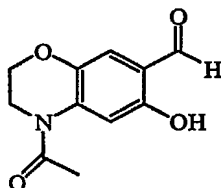


[3α(E), 3A α]

A mixture of intermediate 7 (0.0029 mol), intermediate 2 (0.0035 mol) and NaHCO₃ (0.0043 mol) in 1,4-dioxane (15 ml) was stirred and refluxed for 24 hours. Water was added. This mixture was extracted with CH₂Cl₂. The separated organic layer was dried (Na₂SO₄), filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 9/1, then pure EtOAc).
10 The desired fractions were collected and the solvent was evaporated. The residue was washed with DIPE, then dried. Yield: 0.170 g of intermediate 8 (14%).

Example A.4

Preparation of intermediate 13

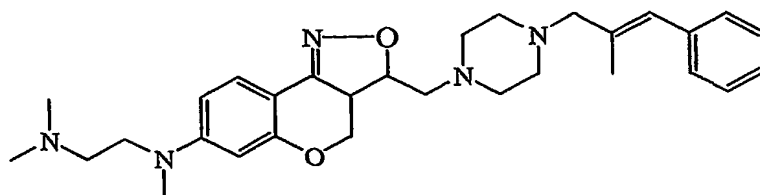


15 A mixture of 4-acetyl-3,4-dihydro-2H-1,4-benzoxazin-6-ol (0.085 mol), MgCl₂ (0.1278 mol), Et₃N (0.3197 mol) and CH₂O (1.023 mol) in CH₃CN (320 ml) was stirred at reflux overnight. The crude reaction was washed with HCl (5%) and extracted with AcOEt. The organic layer was dried over Na₂SO₄, filtered and evaporated till dryness. The residue was purified by open column chromatography with CH₂Cl₂ and
20 CH₂Cl₂:MeOH (1, 2, 4, 10%) as eluents. Yielding 1.13 g of intermediate 13 and 14.99 g of a mixture of starting material and expected product. The reaction was repeated with this mixture (0.077 mol), MgCl₂ (0.1164 mol), Et₃N (0.2909 mol) and CH₂O (0.5237 mol) in CH₃CN (320 ml). It was purified by open column chromatography with CH₂Cl₂:MeOH (1, 2, 4, 10%) as eluents. Yield : 9.34 g of intermediate 13.
25 Total yielding : 10.47 g of intermediate 13 (55%).

B. Preparation of the final compounds

Example B.1

Preparation of compound 1

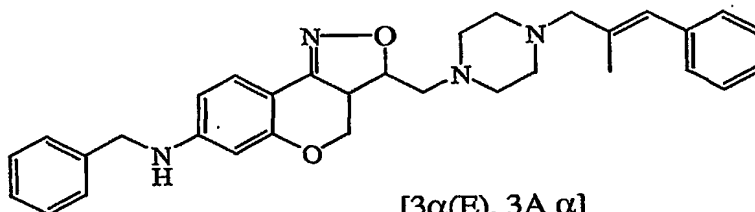


[3 α (E), 3A α]

N,N,N'-trimethyl-1,2-ethanediamine (0.0028469 mol) was added to a solution of intermediate 8 (prepared according to A.3) (0.0002372 mol) in pyridine (2 ml), stirred under N₂ atmosphere. The reaction mixture was stirred and refluxed for 24 hours in a sealed tube. More *N,N,N'*-trimethyl-1,2-ethanediamine (0.0028469 mol) was added and the reaction mixture was stirred for 3 days at 120 °C. The solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2 and 95/5). The product fractions were collected and the solvent was evaporated. Yield: 0.090 g (76%, free base). The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:2) with HCl/2-propanol. The precipitate was filtered off and dried. Yield: 0.045 g of compound 1 (33%).

Example B.2

Preparation of compound 2

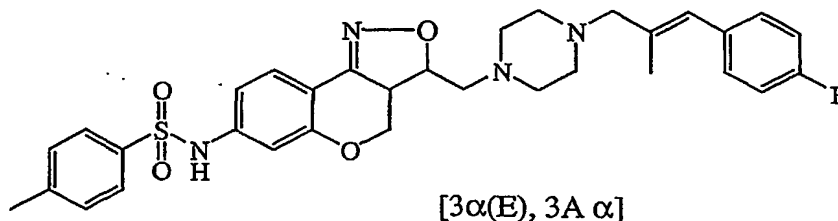


[3 α (E), 3A α]

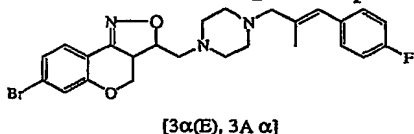
A mixture of intermediate 8 (prepared according to A.3) (0.0024 mol), benzenemethanamine (0.0288 mol) and KF (0.0024 mol) was heated for 5 days at 150 °C in a sealed tube. More benzenemethanamine (0.0288 mol) was added and the reaction mixture was heated at 150 °C for 18 hours. Water was added. This mixture was extracted with CH₂Cl₂. The separated organic layer was dried (Na₂SO₄), filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 2/1). The product fractions were collected and the solvent was evaporated. The residue was washed with DIPE, then dried. Yield: 0.890 g of compound 2 (73%).

Example B.3

Preparation of compound 3



Reaction under N₂ atmosphere. A sealed tube was charged with intermediate 9,

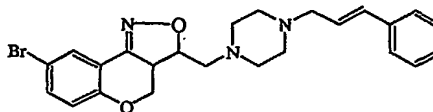
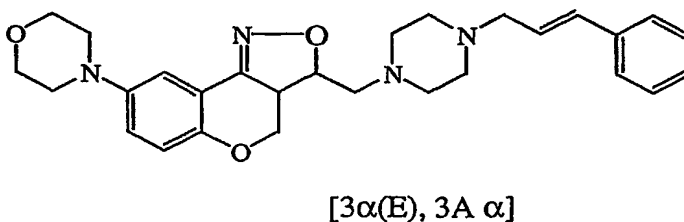


(prepared according to A.3) (0.0003997 mol),

- 4-methylbenzenesulfonamide (0.0004796 mol), Pd(OAc)₂ (0.000004 mol), Xantphos (0.000006 mol) and Cs₂CO₃ (0.0005996 mol) in 1,4-dioxane (2 ml), previously de-oxygenated. The reaction mixture was heated to 100 °C for 24 hours. More Pd(OAc)₂ (0.000012 mol) and Xantphos (0.000018 mol) were added and the reaction mixture was heated for another 24 hours at 100 °C. The reaction mixture was cooled to room temperature, diluted with CH₂Cl₂, filtered through Celite and the filtrate was evaporated. The residue was purified by Sep-Pak Silica Cartridge chromatography (eluent: CH₂Cl₂/(CH₃OH/NH₃) 100/0 and 99/1). The product fractions were collected and the solvent was evaporated. The residue was washed with DIPE, then dried. Yield: 0.100 g of compound 3 (42%). (Xantphos = Phosphine, 9,9-dimethyl-9H-xanthene-4,5-diyl)bis[diphenyl- = CAS 161265-03-8)

15 Example B.4

Preparation of compound 4



A mixture of intermediate 10

(prepared according

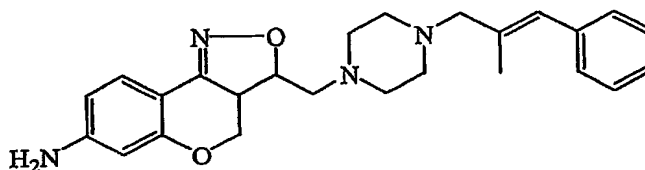
to A.3) (0.0003626 mol), Pd(dba)₂ (0.00001 mol), tributylphosphine (0.000008 mol), *t*-BuONa (0.0004945 mol) and morpholine (0.0003296 mol) in toluene (q.s.) was stirred in a sealed tube under N₂ atmosphere for 24 hours. More morpholine (0.0003296 mol) was added and the reaction mixture was stirred for 24 hours at 100 °C. Then,

water was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue was purified by Sep-Pak Silica Cartridge chromatography (eluent: $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 100/0 and 99/1) and washed with DIPE. Yield : 0.040 g of compound 4 (23%).

5

Example B.5

Preparation of compound 5



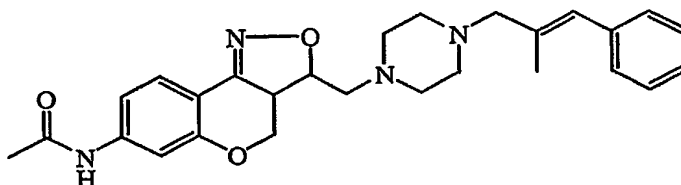
[3 α (E), 3A α]

A mixture of compound 2 (prepared according to B.2) (0.002949 mol) in HBr (25ml) and AcOH (50ml) was warmed at 80°C for 15 days. The reaction mixture was cooled and treated with Na_2CO_3 until pH 7-8, extracted with CH_2Cl_2 and the solvent was evaporated until dry. The residue was purified by short open column chromatography over silica gel (eluent : $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1;98/2). The product fractions were collected and the solvent was evaporated. The residue was washed with DIPE. Yield : 0.5g of compound 5 (41%).

15

Example B.6

Preparation of compound 6



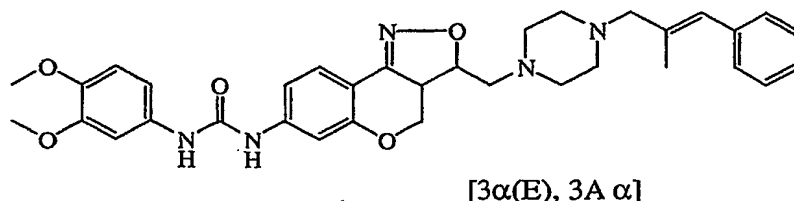
[3 α (E), 3A α]

Methylcarbonylchloride (0.0006451 mol) was added to a mixture of compound 5 (prepared according to B5) (0.0004301 mol) and Et_3N (0.0012903 mol) in CHCl_3 (7 ml), stirred at 0 °C. The reaction mixture was stirred for 2 hours at room temperature. A saturated aqueous NaHCO_3 solution was added. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 97/3 and 96/4). The desired fractions were collected and the solvent was evaporated. Yield: 0.100 g of compound 6 (51%).

25

Example B.7

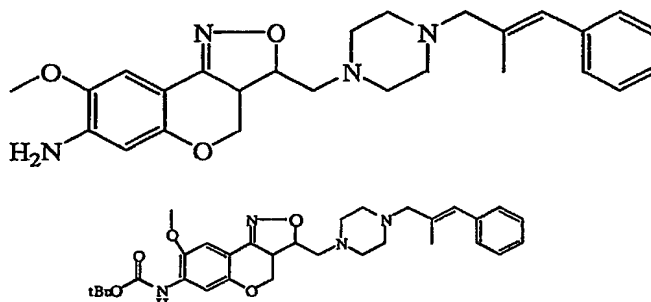
Preparation of compound 7



- 5 4-isocyanato-1,2-dimethoxybenzene (0.0007646 mol) was added to a solution of compound 5 (prepared according to B5) (0.0004779 mol) in THF (3 ml). The reaction mixture was stirred for 24 hours at room temperature. The solvent was evaporated. The residue was purified using Sep-Pak Silica Cartridge chromatography (eluent: CH₂Cl₂/(CH₃OH/NH₃) 99/1 and 98/2). The desired fractions were collected and the solvent was evaporated. The residue was washed with DIPE, then dried. Yield: 0.210 g of compound 7 (73%).

10 Example B.8

Preparation of compound 8

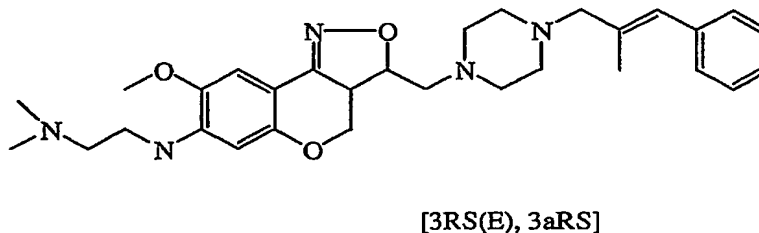


To a solution of intermediate 11 (prepared according to A3) (0.014981 mol) in CH₂Cl₂ (20 ml), TFA (4 ml) was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. Then, the mixture was basified with Na₂CO₃ (saturated solution), extracted with CH₂Cl₂ and evaporated until dryness. The solid was washed with DIPE. Yield: 500 mg of compound 8 (76%).

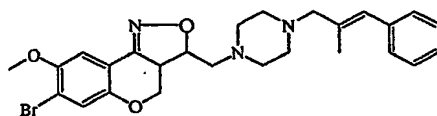
15

Example B.9

Preparation of compound 9



- 20 Reaction under N₂ atmosphere. A sealed tube was charged with Cs₂CO₃ (0.0008196 mol) that had been finely ground and dried in a dessicator. The tube was then charged with Pd(OAc)₂ (0.0391 mmol) and R-BINAP (0.0000527 mol) premixed in de-oxygenated toluene(3 ml).



Then intermediate 12

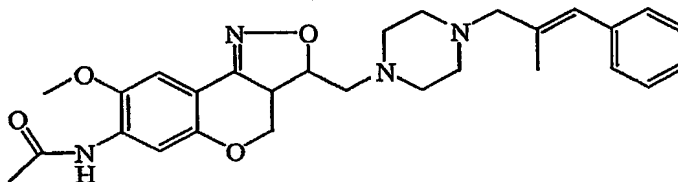
[3RS(E), 3aRS]

(prepared according to A.3)

- (0.0005854 mol) and *N,N*-dimethyl-1,2-ethanediamine (0.0007025 mol) were added and the mixture was heated to 100°C for 24 hours. Then, more *N,N*-dimethyl-1,2-ethanediamine (0.0007025 mol) was added and the mixture was heated to 100°C for 24 hours. The mixture was cooled to room temperature, diluted with CH₂Cl₂, filtered over celite and concentrated. The residue was purified by Sep-Pak Silica Cartridge Chromatography (Eluent: CH₂Cl₂ and CH₂Cl₂/(CH₃OH/NH₃) 1% and 2%) and washed with DIPE. Yield: 107 mg of compound 9 (35%).

Example B.10

Preparation of compound 10

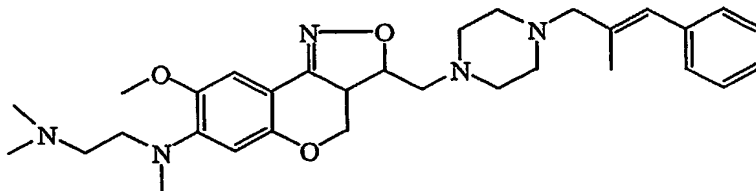


[3α(E), 3αα]

- DIEA, polymer-bound was washed with CHCl₃ (4 ml). After that, a tube was charged with compound 8 (prepared according to B.8) (0.0002229 mol), DIEA (0.0004458 mol) in CHCl₃ (4 ml) and then acetylchloride (0.0002675 mol) was added at 0°C. The mixture was stirred for 3 hours at room temperature. Then, tris(2-aminoethyl)amine, polymer bound (0.0002229 mol) was added and the mixture was stirred overnight at room temperature. The mixture was filtered, concentrated and the residue was washed with DIPE. Yielding : 75 mg of compound 10 (69%).

Example B.11

Preparation of compound 11



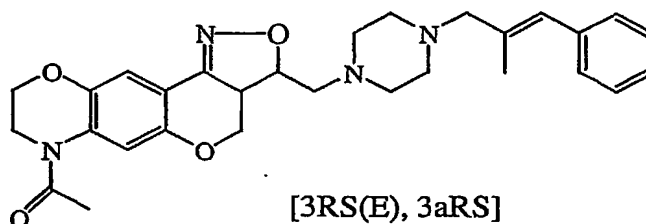
[3α(E), 3αα]

- To a mixture of compound 9 (prepared according to B.9) (0.0002886 mol) and CH₂O (0.0008658 mol) in MeOH (4 ml) was added ZnBr₂ (0.0001443 mol). It was stirred at room temperature for 15 minutes and NaCNBH₃ (0.0004329 mol) was added. The resulting reaction mixture was stirred at reflux for 24 hours. Then, more CH₂O (0.0002886 mol), ZnBr₂ (0.0001443 mol) and NaCNBH₃ (0.0004329 mol) were added

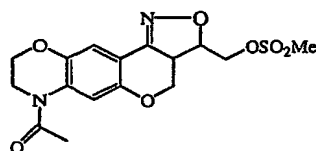
and the reaction mixture was stirred at reflux for 24 hours. Then, more CH₂O (0.0002886 mol), ZnBr₂ (0.0001443 mol) and NaCNBH₃ (0.0004329 mol) were added and the mixture was treated with NH₄Cl (10%) and extracted with CH₂Cl₂. The organic layer was separated, dried (Na₂SO₄) and the solvent evaporated. The residue was
 5 purified by Sep-Pak Silica Cartridge Chromatography (Eluent: CH₂Cl₂ and CH₂Cl₂/(CH₃OH/NH₃) 1%) and liophilized. Yielding : 28 mg of compound 13 (18%).

Example B.12

Preparation of compound 12



A mixture of intermediate 14



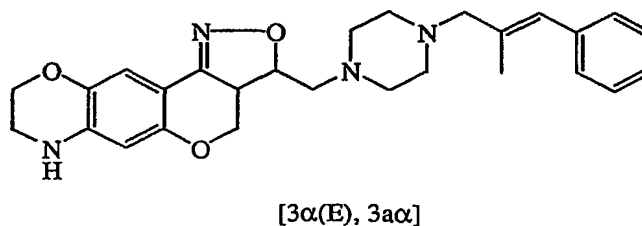
(prepared according to A2.e)

(0.0099 mol), intermediate 2 (prepared according to A1.b) (0.0149 mol), KI (0.0099 mol) and K₂CO₃ (0.0099 mol) in MIK (35 ml) was stirred at reflux overnight. The
 10 crude reaction was evaporated till dryness and the residue was washed with water. It was extracted with AcOEt, dried over Na₂SO₄, filtered and evaporated till dryness. The residue was purified by open column chromatography with CH₂Cl₂:MeOH (4%) as eluent. Yield : 3.1 g of compound 12 (62%).

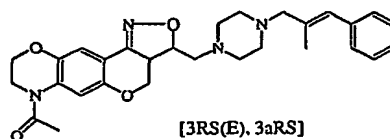
15

Example B.13

Preparation of compound 13



A mixture of compound 12



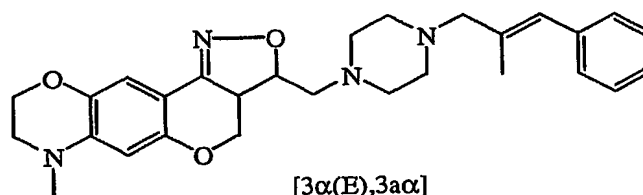
(prepared according to

A.3 with starting material intermediate 13 (prepared according to A.4) instead of 4-fluoro-2-hydroxybenzaldehyde (A2.a)) (0.0046 mol), 15% NaSMc/H₂O (4.41 ml) and

MeOH (42 ml) was stirred at reflux for 2 hours and at room temperature overnight. The crude reaction was concentrated under vacuo and the residue was washed with water and extracted with AcOEt. The organic layer was dried over Na₂SO₄, filtered and evaporated till dryness. The residue was purified by open column chromatography with CH₂Cl₂:MeOH (1, 2, 4 %) as eluents. Finally, the product was crystallized from DIPE. Yield : 0.85 g of compound 12 (39%).

Example B.14

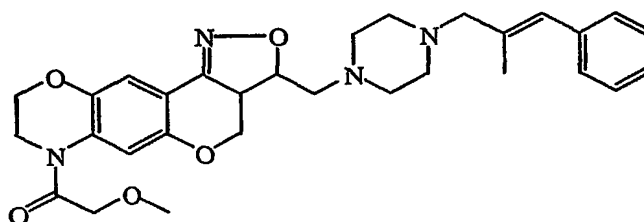
Preparation of compound 14



To a mixture of compound 13 (prepared according to B.13) (0.000217 mol) and CH₂O (0.000217 mol) in sodium cyanoborohydride, 95% (0.00032 mol) in a sealed tube, was added ZnBr₂ (0.0001 mol). It was stirred at room temperature for 15 minutes and MeOH (3 ml) was added. The resulting reaction mixture was stirred at reflux for 2 days. The crude reaction was washed with a 10% NH₄Cl solution and it was extracted with AcOEt. The organic layer was dried over Na₂SO₄, filtered and evaporated till dryness. The residue was purified first, in a manifold under vacuo with a sep-pak silica cartridge (5g) (eluents = CH₂Cl₂ and CH₂Cl₂:MeOH (1,2%)), then, by HPLC with CH₂Cl₂:MeOH (2%) as eluent. Yield : 0.03 g of compound 14 (29%).

Example B.15

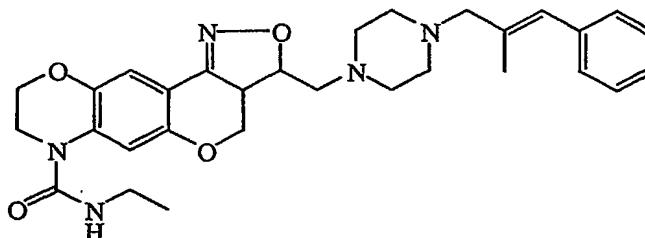
Preparation of compound 15



To a mixture of compound 13 (prepared according to B13) (0.00043 mol) and Et₃N (0.00065 mol) in CHCl₃ (4 ml), cooled with an ice-water bath, was added methoxyacetyl chloride (0.00043 mol) and the resulting reaction mixture was stirred at room temperature overnight. The crude reaction was washed with a saturated NaHCO₃ solution and it was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and evaporated till dryness. The residue was purified in a manifold under vacuo with a sep-pak silica cartridge (5 g) (eluents = CH₂Cl₂:acetone (10%) and CH₂Cl₂:MeOH (2%)). Finally, the product crystallized with DIPE. Yield : 0.6782 g of compound 15 (34%).

Example B.16

Preparation of compound 16

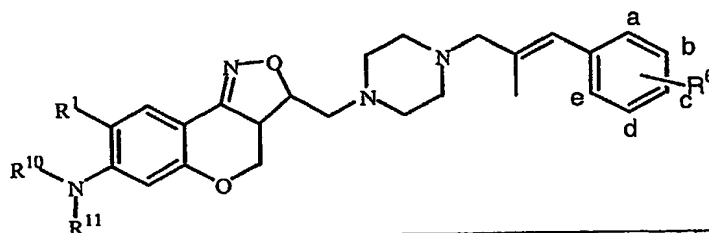


5 A mixture of compound 13 (prepared according to B13) (0.00026 mol), EtNCO (0.00041 mol) and toluene (3 ml) was stirred at 75°C overnight, in a sealed tube. The solvent was evaporated and the residu was purified in a manifold under vacuo with a sep-pak silica cartridge (5 g) (eluent = CH₂Cl₂, CH₂Cl₂:acetone 10% and CH₂Cl₂:MeOH 2%). Finally, the product as a syrup was crystallized from DIPE. Yield 0.0595 g of compound 16 (43%).

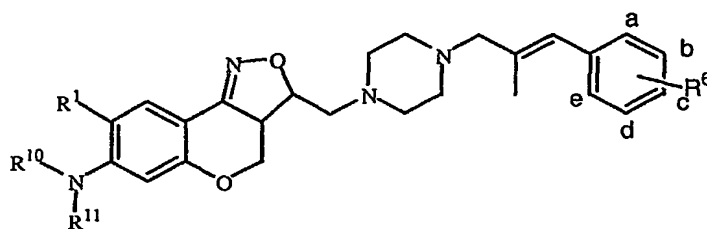
10

15 In the following tables (Tables 1-4) a number of compounds are given which have been prepared according to any one of the Examples above. All compounds have also been tested for their pharmacological activity.

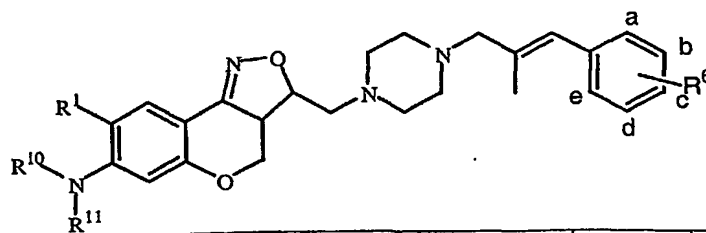
Table 1 :



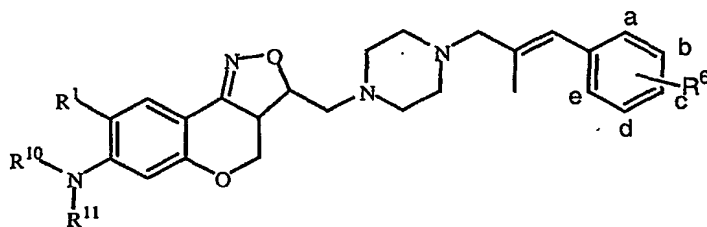
Comp nr.	Ex. nr.	R ¹	-R ¹⁰	R ¹¹	R ⁶	Phys.data
5	B5	H	H	H		[3α(E), 3αα]
8	B8	OCH ₃	H	H		[3α(E), 3αα]
86	B8	OCH ₃	H	H	b-F	[3α(E), 3αα]
87	B5	H	--CH ₃	H		[3α(E), 3αα] HCl (1:2)
88	B11	OCH ₃	--CH ₃	H		[3α(E), 3αα]
17	B11	OCH ₃	--CH ₃	H	b-F	[3α(E), 3αα]
18	B1	H	--CH ₂ CH ₃	H		[3α(E), 3αα]
19	B1	H		CH ₃	c-F	[3α(E), 3αα] HCl (1:1)
20	B1	H		H	c-F	[3α(E), 3αα] HCl (1:1)
21	B1	H		CH ₃	c-F	[3α(E), 3αα]
1	B1	H		CH ₃	-	[3α(E), 3αα] HCl (1:2)
22	B1	H		CH ₃	b-F	[3α(E), 3αα] HCl (1:2)
23	B1	H		CH ₃	c-F	[3α(E), 3αα] HCl (1:1)
9	B9	OCH ₃		H		[3α(E), 3αα]
24	B9	OCH ₃		H	c-F	[3α(E), 3αα]
11	B11	OCH ₃		CH ₃		[3α(E), 3αα]
25	B1	H		CH ₃	c-F	[3α(E), 3αα] HCl (1:1)



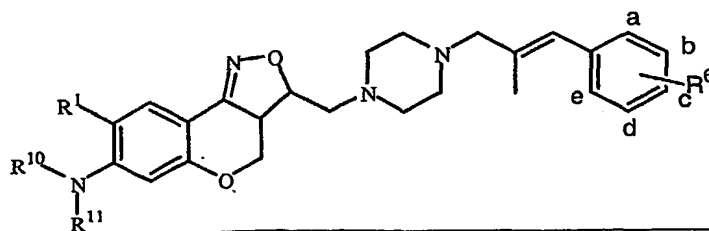
Comp nr.	Ex. nr.	R ¹	--R ¹⁰	R ¹¹	R ⁶	Phys.data
26	B9	OCH ₃		H		[3α(E), 3αα]
27	B9	OCH ₃		H	b-F	[3α(E), 3αα]
28	B1	H		H	c-F	[3α(E), 3αα]
29	B9	OCH ₃		H	c-F	[3α(E), 3αα]
30	B1	H		H	c-F	[3α(E), 3αα]
31	B1	H		CH ₃		[3α(E), 3αα]
32	B9	OCH ₃		CH ₃		[3α(E), 3αα]
33	B1	H		CH ₃		A-[3α(E), 3αα]
34	B1	H		CH ₃		B-[3α(E), 3αα]
35	B1	H		CH ₃	b-F	[3α(E), 3αα]
36	B9	OCH ₃		CH ₃	b-F	[3α(E), 3αα]
37	B1	H		H	c-F	[3α(E), 3αα]
38	B1	H		CH ₃	c-F	[3α(E), 3αα]
39	B9	OCH ₃		CH ₃	c-F	[3α(E), 3αα]
40	B2	H		H		[3α(E), 3αα]
41	B2	H		CH ₃		[3α(E), 3αα]
42	B2	H		H		[3α(E), 3αα]



Comp nr.	Ex. nr.	R ¹	--R ¹⁰ --	R ¹¹	R ⁶	Phys.data
43	B2	H		H	c-F	[3α(E), 3αα]
44	B2	H		H		[3α(E), 3αα]
45	B2	H		H		[3α(E), 3αα]
46	B2	H		H		[3α(E), 3αα]
47	B1	H		CH ₃		[3α(E), 3αα]
48	B1	H		CH ₃		[3α(E), 3αα] HCl(1:2)
2	B1	H		H		[3α(E), 3αα]
6	B6	H		H		[3α(E), 3αα]
10	B10	OCH ₃		H		[3α(E), 3αα]
49	B10	OCH ₃		H	b-F	[3α(E), 3αα]
50	B6	H		H		[3α(E), 3αα]
51	B6	H		H		[3α(E), 3αα]

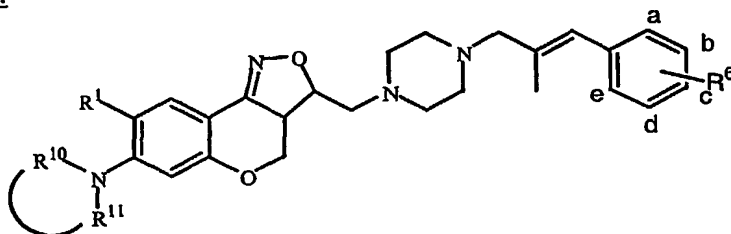


Comp nr.	Ex. nr.	R ¹	-R ¹⁰	R ¹¹	R ⁶	Phys.data
52	B10	OCH ₃		H		[3α(E), 3αα]
53	B10	OCH ₃		H	b-F	[3α(E), 3αα]
54	B6	H		H		[3α(E), 3αα]
55	B6	H		H		[3α(E), 3αα]
56	B6	H		H		[3α(E), 3αα, 7(R)]
57	B6	H		H		[3α(E), 3αα, 7(S)]
58	B6	H		H	c-F	[3α(E), 3αα]
59	B7	H		H		[3α(E), 3αα]
60	B7	H			c-F	[3α(E), 3αα]
61	B7	H		H		[3α(E), 3αα]
62	B7	H		H		[3α(E), 3αα]
63	B7	H		H		[3α(E), 3αα]

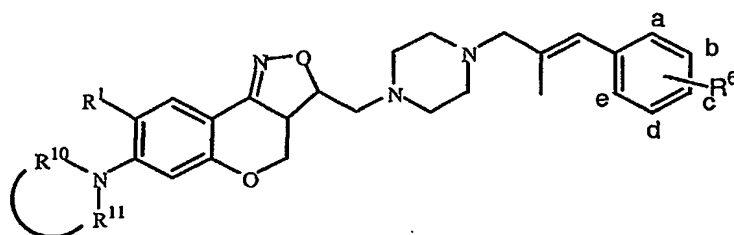


Comp nr.	Ex. nr.	R ¹	—R ¹⁰	R ¹¹	R ⁶	Phys.data
64	B7	H		H		[3α(E), 3α]
65	B7	H		H		[3α(E), 3α]
7	B7	H		H		[3α(E), 3α]
66	B6	H	—SO ₂ CH ₃	—SO ₂ CH ₃		[3α(E), 3α]
3	B3	H		H	c-F	[3α(E), 3α]
67	B6	H		H		[3α(E), 3α]
68	B7	H		H	c-F	[3α(E), 3α]

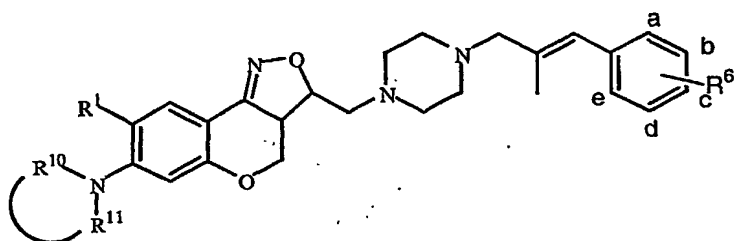
Table 2:



Comp nr.	Ex. nr.	R ¹		R ⁶	Phys.data
69	B1	H		c-F	[3α(E), 3α]

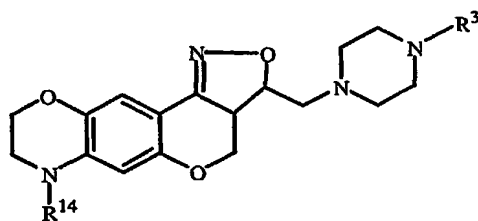


Comp nr.	Ex. nr.	R ¹		R ⁶	Phys.data
70	B1	H		c-F	[3α(E), 3αα]
71	B1	H		c-F	[3α(E), 3αα]
72	B1	H		c-F	[3α(E), 3αα]
73	B1	H		c-F	[3α(E), 3αα]
74	B1	H		c-F	[3α(E), 3αα]
75	B9	OCH ₃			[3α(E), 3αα]
76	B9	OCH ₃		b-F	[3α(E), 3αα]
77	B1	H		c-F	[3α(E), 3αα]
78	B9	OCH ₃		c-F	[3α(E), 3αα]
79	B1	H		c-F	[3α(E), 3αα]
80	B1	H		c-F	[3α(E), 3αα]
81	B3	H		c-F	[3α(E), 3αα, 7(E)]
82	B9	OCH ₃			[3α(E), 3αα]

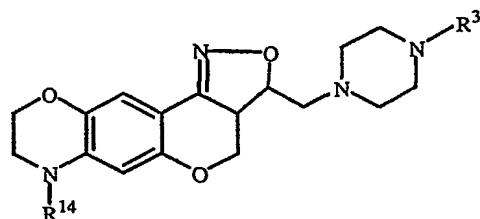


Comp nr.	Ex. nr.	R¹		R⁶	Phys.data
83	B9	OCH₃		b-F	[3α(E), 3α]
84	B1	H		c-F	[3α(E), 3α]
85	B9	OCH₃		c-F	[3α(E), 3α]

Table 3:

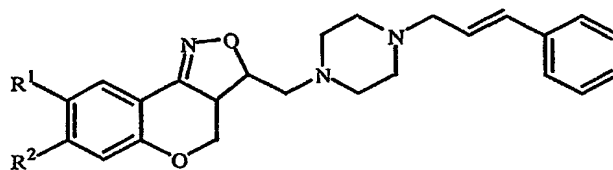


Comp nr.	Ex. nr.	R¹⁴	R³	Phys.data
13	B12	H		[3α(E), 3α]
89	B12	H		[3α(E), 3α]
90	B12	H		[3α(E), 3α]
91	B12	H		[3α(E), 3α]



Comp nr.	Ex. nr.	R ¹⁴	R ³	Phys.data
92	B12	H		cis
14	B14	CH ₃		[3α(E), 3αα]
12	A3			[3α(E), 3αα]
15	B15			[3α(E), 3αα]
16	B16			[3α(E), 3αα]
94	B12	H		(CIS)

Table 4



Comp. nr.	Ex. nr.	--R ¹	--R ²	Phys.data - configuration
4	B4		H	[3α(E), 3αα]
93	B4		H	[3α(E), 3αα]

C. Pharmacological examples

Example C1 : Binding experiment for α_2 -adrenergic receptor subtypes and for 5-HT transporter

5 General

The interaction of the compounds of Formula (I) with α_2 -receptors and h5-HT-transporters was assessed in *in vitro* radioligand binding experiments. In general, a low concentration of a radioligand with a high binding affinity for a particular receptor or transporter is incubated with a sample of a tissue preparation enriched in a particular
10 receptor or transporter or with a preparation of cells expressing cloned human receptors in a buffered medium. During the incubation, the radioligand binds to the receptor or transporter. When equilibrium of binding is reached, the receptor bound radioactivity is separated from the non-bound radioactivity, and the receptor- or transporter-bound activity is counted. The interaction of the test compounds with the receptor is assessed
15 in competition binding experiments. Various concentrations of the test compound are added to the incubation mixture containing the receptor- or transporter preparation and the radioligand. The test compound in proportion to its binding affinity and its concentration inhibits binding of the radioligand. The radioligand used for α_{2A} , α_{2B} and α_{2C} receptor binding was [^3H]-rauwolscine and for the h5-HT transporter
20 was [^3H]paroxetine.

Cell culture and membrane preparation.

CHO cells, stable transfected with human adrenergic- α_{2A} -, α_{2B} or α_{2C} receptor cDNA, were cultured in Dulbecco's Modified Eagle's Medium (DMEM)/Nutrient mixture
25 Ham's F12 (ratio 1:1)(Gibco, Gent-Belgium) supplemented with 10 % heat inactivated fetal calf serum (Life Technologies, Merelbeke-Belgium) and antibiotics (100 IU/ml penicillin G, 100 $\mu\text{g/ml}$ streptomycin sulphate, 110 $\mu\text{g/ml}$ pyruvic acid and 100 $\mu\text{g/ml}$ L-glutamine). One day before collection, cells were induced with 5 mM sodiumbutyrate. Upon 80-90 % of confluence, cells were scraped in phosphate
30 buffered saline without Ca^{2+} and Mg^{2+} and collected by centrifugation at 1500 x g for 10 min. The cells were homogenised in Tris-HCl 50 mM using an Ultraturrax

homogenizer and centrifuged for 10 min at 23,500 x g. The pellet was washed once by resuspension and rehomogenization and the final pellet was resuspended in Tris-HCl , divided in 1 ml aliquots and stored at -70°C.

5 Binding experiment for α_2 -adrenergic receptor subtypes

Membranes were thawed and re-homogenized in incubation buffer (glycylglycine 25 mM, pH 8.0). In a total volume of 500 μ l, 2-10 μ g protein was incubated with [3 H]rauwolscine (NET-722) (New England Nuclear, USA) (1 nM final concentration) with or without competitor for 60 min at 25°C followed by rapid filtration over GF/B
10 filter using a Filtermate196 harvester (Packard, Meriden, CT). Filters were rinsed extensively with ice-cold rinsing buffer (Tris-HCl 50 mM pH 7.4). Filter-bound radioactivity was determined by scintillation counting in a Topcount (Packard, Meriden, CT) and results were expressed as counts per minute (cpm). Non-specific binding was determined in the presence of 1 μ M oxymetazoline for $h\alpha_{2A}$ - and $h\alpha_{2B}$
15 receptors and 1 μ M spiroxatrine for $h\alpha_{2C}$ receptors.

Binding experiment for 5-HT transporter

Human platelet membranes (Oceanix Biosciences Corporation, Hanover, MD, USA) were thawed, diluted in buffer (Tris-HCl 50 mM, 120 mM NaCl and 5 mM KCl) and
20 quickly (max 3 s) homogenised with an Ultraturrax homogenizer. In a total volume of 250 μ L, 50-100 μ g protein was incubated with [3 H]paroxetine (NET-869) (New England Nuclear, USA) (0.5 nM final concentration) with or without competitor for 60 min at 25 °C . Incubation was stopped by rapid filtration of the incubation mixture over GF/B filters, pre-wetted with 0.1 % polyethylenamine, using a Filtermate196 harvester
25 (Packard, Meriden, CT). Filters were rinsed extensively with ice-cold buffer and radioactivity on the filters was counted in a Topcount liquid scintillation counter (Packard, Meriden, CT). Data were expressed as cpm. Imipramine (at 1 μ M final concentration) was used to determine the non-specific binding.

30 Data analysis and results

Data from assays in the presence of compound were calculated as a percentage of total binding measured in the absence of test compound. Inhibition curves, plotting percent of total binding versus the log value of the concentration of the test compound, were

of total binding versus the log value of the concentration of the test compound, were automatically generated, and sigmoidal inhibition curves were fitted using non-linear regression. The pIC_{50} values of test compounds were derived from individual curves.

All compounds according to formula (I) produced an inhibition at least at the $h\alpha_2A$ site (but often also at the $h\alpha_2B$ and $h\alpha_2C$ sites) and simultaneously at the 5-HT transporter site of more than 50 % (pIC_{50}) at a test concentration ranging between 10^{-6} M and 10^{-9} M in a concentration-dependent manner. Results are shown in Table 5.

10 Table 5 : pIC_{50} -values for the $h\alpha_2A$ and 5-HT transporter receptor site.

Comp. nr.	pIC_{50}		
	α_2A	α_2C	h5HTT
1	8.9	9	8.2
2	7.8	8.1	7.5
31	8.9	8.9	7.6
48	7.4	7.5	6.8
47	8.6	8.5	7.3
87	8.6	8.5	7.3
5	8.6	8.4	7.0
6	8.5	8.6	7.3
64	7.6	7.8	6.6
38	7.1	8.8	7.9
23	8.0	8.7	8.3
70	7.9	8.1	7.0
71	7.2	8.2	7.0
37	8.5	8.3	7.2
28	7.2	8.4	8.5
30	7.3	8.4	8.0
73	7.3	8.3	7.2
74	6.9	8.2	6.8
77	7.4	8.6	8.5
84	8.2	8.9	7.6
72	7.0	7.7	6.2

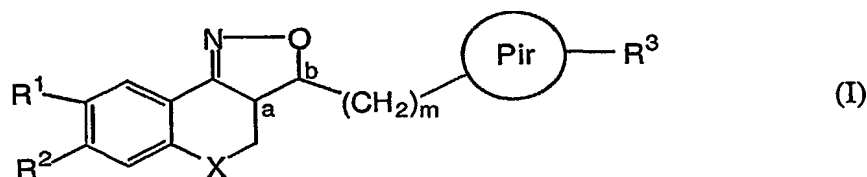
Comp. nr.	pIC_{50}		
	α_2A	α_2C	h5HTT
21	8.1	8.7	8.4
25	8.2	9.4	8.1
79	6.6	8.1	6.7
80	6.9	8.4	6.9
19	7.9	8.6	8.0
20	7.5	8.5	8.1
4	7.9	8.6	<6
58	7.2	7.5	7.5
93	7.7	7.2	6.4
43	6.4	6.9	6.2
81	6.9	7.7	7.2
35	8.5	8.9	8.1
22	8.8	8.9	8.8
3	7.1	7.5	7.4
68	7.4	7.7	7.8
69	8.5	8.9	7.7
75	8.8	>9	8.1
26	8.3	>9	8.5
82	8.8	8.9	7.4
60	5.5	6.4	5.2
32	8.4	9.1	7.7

Comp. nr.	pIC ₅₀		
	α 2A	α 2C	h5HTT
78	8.0	8.7	8.1
40	7.8	8.0	7.3
44	7.8	7.7	7.8
45	7.7	7.7	7.1
41	7.6	7.6	6.8
42	7.5	7.8	6.9
46	7.2	7.4	6.5
9	8.3	6.0	8.3
24	7.6	8.8	8.3
33	6.2	7.4	7.9
34	8.7	9.4	7.2
7	7.8	8.3	7.5
65	7.1	7.5	5.8
66	8.3	9.3	7.4
54	8.8	9.1	7.6
55	8.3	8.5	7.6
51	8.8	9.0	7.8
67	8.7	8.9	7.9
50	8.5	9.0	7.8
63	8.1	8.8	7.5
62	7.6	8.2	7.4
61	8.1	8.7	7.7
12	8.7	9.0	7.5
13	8.4	9.2	7.9
85	8.0	8.5	7.2
29	7.8	8.8	8.5
90	7.8	8.8	7.8
89	8.4	9.0	8.4
92	7.7	8.6	8.3
94	6.5	7.5	6.9
91	8.2	8.8	7.5
15	8.5	9.1	8.0
59	8.1	8.9	8.0
76	8.4	9.1	8.5
16	8.1	9.1	8.1

Comp. nr.	pIC ₅₀		
	α 2A	α 2C	h5HTT
27	7.8	8.5	8.3
83	8.1	8.6	7.8
14	7.8	8.3	7.5
8	8.3	8.8	7.6
10	8.4	8.9	7.2
86	8.2	8.8	8.3
11	8.7	8.8	8.5
56	8.5	9.3	7.9
52	8.4	9.2	7.7
49	8.9	9.6	8.1
53	8.4	9.2	8.0
57	8.3	9.2	7.6
88	8.3	8.9	7.7
17	8.1	8.7	7.9
18	8.2	8.9	7.3
39	7.3	8.0	7.1
36	7.7	8.6	7.6

Claims

1. A compound according to the general Formula (I)



- 5 the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the *N*-oxide form thereof, wherein :

X is CH₂, N-R⁷, S or O ;

R⁷ is selected from the group of hydrogen, alkyl, Ar¹, Ar¹alkyl, alkylcarbonyl, alkyloxycarbonyl and mono- and di(alkyl)aminocarbonyl ;

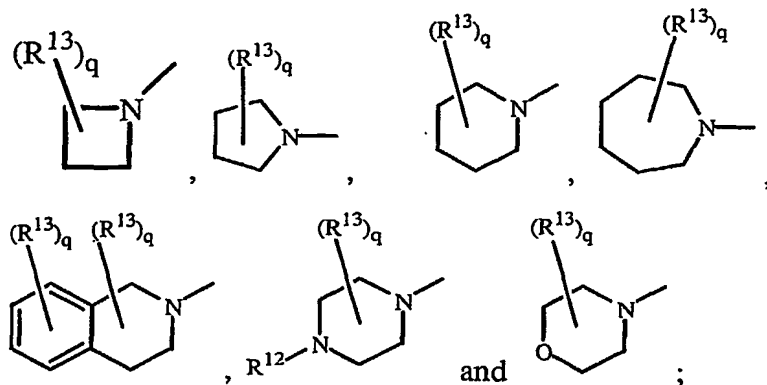
- 10 R¹ and R² are each selected from the group of hydrogen, hydroxy, cyano, halo, OSO₂H, OSO₂CH₃, N-R¹⁰R¹¹, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkylthio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenylcarbonyloxy and mono- or di(alkyl)aminoalkyloxy ;

15 with the proviso that at least one of R¹ and R² is N-R¹⁰R¹¹ wherein :

R¹⁰ and R¹¹ are each, independently from each other, selected from the group of hydrogen, alkyl, Ar¹, Ar¹alkyl, pyrrolidinylalkyl, piperidinylalkyl, homopiperidinylalkyl, piperazinylalkyl, morpholinylalkyl, mono- or di(alkyl)aminoalkyl, alkylcarbonyl, alkenylcarbonyl, Ar¹carbonyl, pyridinylcarbonyl, alkyloxycarbonyl, mono- or di(alkyl)aminocarbonyl, mono- or di(Ar¹)aminocarbonyl, mono- or di(alkyloxycarbonylalkyl)aminocarbonyl, pyrrolidinylcarbonyl, aminoiminomethyl, alkylaminoiminomethyl, N-benzylpiperazinylimino-

20 methyl, alkylsulphonyl and Ar¹sulphonyl ; or

- 25 R¹⁰ and R¹¹ may be taken together and with the N may form a monovalent radical selected from the group of



wherein :

5 R^{12} is selected from the group of hydrogen, alkyl, Ar^1 , Ar^1 alkyl, Ar^1 alkenyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

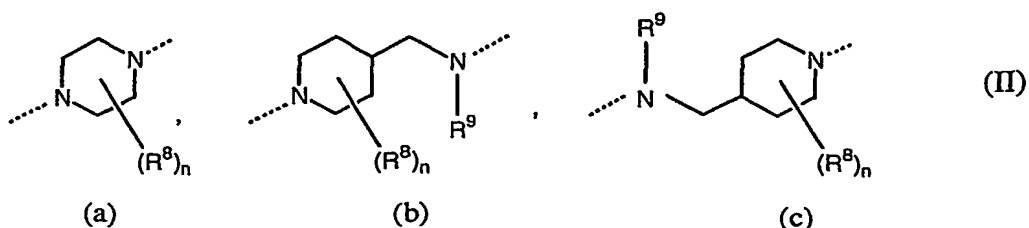
each ring being optionally substituted with q radicals R^{13} , each radical independently from each other selected from the group of alkyl, oxo, Ar^1 , Ar^1 alkyl, Ar^1 alkenyl and alkyloxycarbonyl and q being an integer ranging from 0 to 6 ; or

10 R^1 and R^2 may be taken together to form a bivalent radical $-R^1-R^2-$ selected from the group of $-O-CH_2-NR^{14}-$, $-NR^{14}-CH_2-O-$, $-NR^{15}-CH_2-NR^{14}-$, $-NR^{14}-CH_2-CH_2-O-$, $-O-CH_2-CH_2-NR^{14}-$, $-NR^{15}-CH_2-CH_2-NR^{14}-$, - wherein R^{14} and R^{15} each, independently from each other, are selected from the group of hydrogen, alkyl, Ar^1 , Ar^1 alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkylcarbonyl and mono- or di(alkyl)aminocarbonyl ;

a and b are asymmetric centers ;

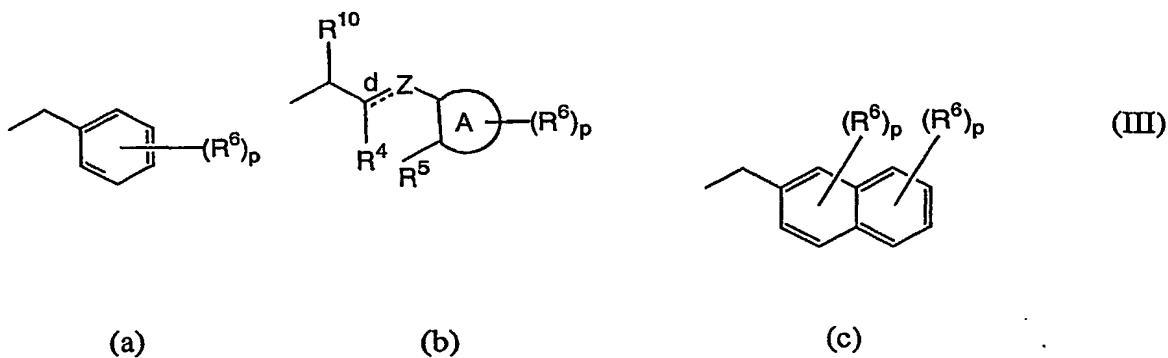
15 $(CH_2)_m$ is a straight hydrocarbon chain of m carbon atoms, m being an integer ranging from 1 to 4 ;

Pir is a radical according to any one of Formula (IIa), (IIb) or (IIc)



- optionally substituted with n radicals R^8 , wherein :
- each R^8 is independently from each other, selected from the group of hydroxy, amino, nitro, cyano, halo and alkyl ;
- n is an integer ranging from 0 to 5 ;
- R^9 is selected from the group of hydrogen, alkyl and formyl ;
- R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system together with an optionally substituted and partially or completely hydrogenated hydrocarbon chain of 1 to 6 atoms long with which said ring system is attached to the Pir radical and of which may contain one or more heteroatoms selected from the group of O, N and S ;
- alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyloxy or amino radicals ;
- alkenyl represents a straight or branched unsaturated hydrocarbon radical having one or more double bonds, optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyloxy or amino radicals ;
- Ar^1 represents phenyl or naphthyl, optionally substituted with one or more halo, cyano, oxo, hydroxy, alkyl, alkyloxy or amino radicals.

2 A compound according to claim 1, characterized in that R^3 is a radical according to any one of Formula (IIIa), (IIIb) or (IIIc)



wherein :

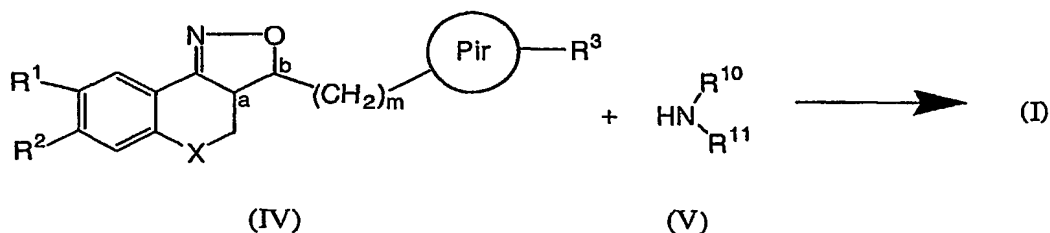
- d is a single bond while Z is a bivalent radical selected from the group of -CH₂-, -C(=O)-, -CH(OH)-, -C(=N-OH)-, -CH(alkyl)-, -O-, -S-, -S(=O)-, -NH- and -SH-; or d is a double bond while Z is a trivalent radical of formula =CH- or =C(alkyl)- ;
- A is a 5- or 6-membered aromatic homocyclic or heterocyclic ring, selected from the group of phenyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, oxadiazolyl and isoxazolyl ;
- p is an integer ranging from 0 to 6 ;
- R⁴ and R⁵ are each, independently from each other, selected from the group of hydrogen, alkyl, Ar¹, biphenyl, halo and cyano ; or
- R⁴ and R⁵ may be taken together to form a bivalent radical -R⁴-R⁵- selected from the group of -CH₂-, =CH-, -CH₂-CH₂-, -CH=CH-, -O-, -NH-, =N-, -S-, -CH₂N(-alkyl)-, -N(-alkyl)CH₂-, -CH₂NH-, -NHCH₂-, -CH=N-, -N=CH-, -CH₂O- and -OCH₂- ;
- each R⁶ is independently from each other, selected from the group of hydroxy, amino, nitro, cyano, halo, carboxyl, alkyl, Ar¹, alkyloxy, Ar¹oxy, alkyl-carbonyloxy, alkyloxycarbonyl, alkylthio, mono- and di(alkyl)amino, alkylcarbonylamino, mono- and di(alkyl)aminocarbonyl, mono- and di(alkyl)aminocarbonyloxy, mono- and di(alkyl)aminoalkyloxy ; or
- two vicinal radicals R⁶ may be taken together to form a bivalent radical -R⁶-R⁶- selected from the group of -CH₂-CH₂-O-, -O-CH₂-CH₂-, -O-CH₂-C(=O)-, -C(=O)-CH₂-O-, -O-CH₂-O-, -CH₂-O-CH₂-, -O-CH₂-CH₂-O-, -CH=CH-CH=CH-, -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-C(=O)-, -C(=O)-CH₂-CH₂-, -CH₂-C(=O)-CH₂- and -CH₂-CH₂-CH₂-CH₂- ; and
- R¹⁰ is selected from the group of hydrogen, alkyl, Ar¹ and Ar¹alkyl.
3. A compound according to any of claims 1-2, characterized in that X=O or NH ; m = 1 ; Pir is a radical according to Formula (IIa) wherein n = 0 ; R³ is a radical according to Formula (IIIb) wherein Z is =CH-, d is a double bond, A is a

phenyl ring, R⁴ is hydrogen or alkyl and R⁵ and R¹⁰ are each hydrogen.

4. A compound according to any one of claims 1-3 for use as a medicine.
- 5 5. A compound which is degraded *in vivo* to yield a compound according to any one of claims 1-3.
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient a therapeutically effective amount of a compound
10 according to any one of claims 1 - 3 or a compound according to claim 5.
7. A process for making a pharmaceutical composition according to claim 6, comprising mixing a compound according to any one of claims 1-3 or a compound according to claim 5 and a pharmaceutically acceptable carrier:
15 ..
8. The use of a compound according to any one of claims 1 -3 or a compound according to claim 5 for the manufacture of a medicament for treating depression, anxiety and body weight disorders.
- 20 9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient a therapeutically effective amount of a compound according to any one of claims 1-3 or a compound according to claim 5 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.
25
10. The use of a pharmaceutical composition according to claim 9 for the manufacture of a medicament to improve efficacy and/or onset of action in the treatment of depression, anxiety and body weight disorders.
- 30 11. The use of a compound according to any one of claims 1-3 or a compound according to claim 5 for the manufacture of a medicament for the treatment of depression, anxiety and body weight disorders, said treatment comprising the simultaneous or sequential administration of a compound according to any one

of claims 1-3 or a compound according to claim 5 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.

- 5 12. The use of one or more compounds selected from the group of antidepressants, anxiolytics and antipsychotics for the manufacture of a medicament for the treatment of depression, anxiety and body weight disorders, said treatment comprising the simultaneous or sequential administration of one or more compounds selected from the group of antidepressants, anxiolytics and antipsychotics and a compound according to any one of claims 1-3 or a compound according to claim 5.
- 10 13. The use of a pharmaceutical composition according to claim 9 to improve efficacy and/or onset of action in the treatment of depression, anxiety and body weight disorders.
- 15 14. A process for making a pharmaceutical composition according to claim 9, comprising mixing a compound according to any one of claims 1-3 or a compound according to claim 5 and a compound selected from the group of antidepressants, anxiolytics and antipsychotics and a pharmaceutically acceptable carrier.
- 20 15. A process for preparing a compound according to Formula (I), characterized in that a compound according to Formula (IV) is reacted with an amine of Formula (V) according to the following reaction
- 25

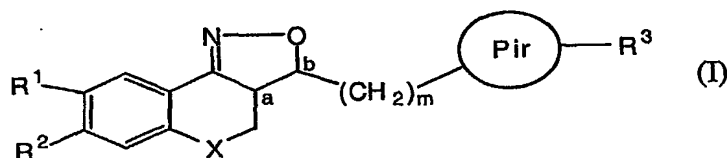


wherein all variables, except for R¹ and R², have the same meaning as in

5 Formula (I), at least one of R^1 and R^2 is an halogen and at most one of R^1 and R^2 is selected from the group of hydrogen, hydroxy, cyano, halo, OSO_2H , OSO_2CH_3 , $N-R^{10}R^{11}$, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkylthio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenylcarbonyloxy and mono-or di(alkyl)aminoalkyloxy.

ABSTRACT
AMINO ISOXAZOLINE DERIVATIVES AND THEIR USE AS
ANTI-DEPRESSANTS

5 The invention concerns substituted amino isoxazoline derivatives, more in particular tricyclic dihydrobenzopyranoisoxazoline, dihydroquinolinoisoxazoline, dihydronaphthalenoisoxazoline and dihydrobenzothiopyranoisoxazoline derivatives substituted on the phenylpart of the tricyclic moiety with primary, secondary and/or
10 tertiary amino groups, according to Formula (I)



wherein X = CH₂, N-R⁷, S or O, R¹, R² and R³ are certain specific substituents, with the proviso that at least one of R¹ and R² is an amino radical of formula N-R¹⁰R¹¹ wherein R¹⁰ and
15 R¹¹ are each a variety of radicals, Pir is an optionally substituted piperidyl or piperazyl radical and R³ represents an optionally substituted aromatic homocyclic or heterocyclic ring system including a partially or completely hydrogenated hydrocarbon chain of maximum 6 atoms long with which the ring system is attached to the Pir radical and which may contain one or more heteroatoms selected from the group of O, N and S ; a process for their preparation,
20 pharmaceutical compositions comprising them and their use as a medicine, in particular for the treatment of depression and/of anxiety and disorders of body weight. The compounds according to the invention have surprisingly been shown to have a serotonin (5-HT) reuptake inhibitor activity in combination with additional α₂-adrenoceptor antagonist activity and show a strong anti-depressant activity without being sedative. Compounds according to the invention
25 are also suitable for treating depression, anxiety and body weight disorders. The invention also relates to novel combination of substituted amino isoxazoline derivatives according to the invention with antidepressants, anxiolytics and/or antipsychotics to improve efficacy and/or onset of action.

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~ 2. 04. 2002

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